

THE EFFECT OF SOME PHYSIOLOGICAL FACTORS AND PHARMACOLOGICAL
AGENTS ON LEFT VENTRICULAR FUNCTION IN MAN

by

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Thesis presented for the Degree of Doctor of Philosophy of the
University of Edinburgh in the Faculty of Medicine

1st September, 1966.



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A C K N O W L E D G M E N T S

I wish to express my gratitude to Professor K. W. Donald for the encouragement, advice, and helpful criticisms liberally offered to me throughout the whole period of this work. I wish also to thank him for affording me every possible facility in the pursuit of these investigations.

I am greatly indebted to my colleagues for their ungrudging assistance and also many stimulating discussions which have aided in the formulation of my thoughts. In particular I should like to thank Drs. S. H. Taylor and H. R. Macdonald for their invaluable help.

I should also like to express my deep appreciation for the willing assistance given to me by the nursing and technical staff.

The opportunity to pursue this work was given to me following the grant of a Commonwealth Scholarship by the Commonwealth Scholarships Commission and the Association of Commonwealth Universities, and I am grateful for the financial support received.

I should also like to express my grateful thanks to Mrs. L. Brock, Miss M. Down and Miss E. O. McKeating for their painstaking care in typing the manuscript.

INTRODUCTION

In recent years, significant conceptual advances have helped to formulate a broad scheme of the mechanisms which regulate ventricular function.

Likewise, methodological advances now enable a wide range of haemodynamic measurements to be made in human subjects, with reasonable precision and relative ease. It has thus become possible to relate changes in several haemodynamic variables recorded simultaneously.

Although it is still not feasible to estimate the functional competence of the left ventricle (or the heart as a whole) in absolute terms, the qualitative changes can now be assessed with greater confidence.

The studies reported here were designed to investigate the changes in left ventricular performance in man during dynamic exercise and following the administration of two pharmacological agents used in clinical practice.

The two pharmacological agents, morphine and propranolol, were selected for different reasons.

Morphine was chosen in order to determine the circulatory effects that may be attributable to the drug and thereby provide, if possible, a rational basis for its use in the treatment of acute left ventricular failure. The therapeutic efficacy of morphine in this disorder is widely acknowledged, but to date no attempts, other than the one reported here, seem to have been made, (or at least none reported) to delineate the precise mode of action of this drug in the treatment of acute left ventricular failure. A detailed investigation was, therefore, designed to study the haemodynamic changes, with particular reference to left ventricular function, following an intravenous injection of morphine in therapeutic amounts. The report on this study forms the subject matter of Chapter IV.

The other pharmacological agent used was propranolol, which is an adrenergic β -receptor blocking agent. It is generally agreed that the

sympathetic nervous system (and the adrenal medulla) dominates in the regulation of the cardiovascular response during dynamic exercise. Since the sympathetic influence (both chronotropic and inotropic) on the heart is mediated through β -receptors (Ahlquist, 1948), it was felt that with the help of propranolol it should be possible to assess the importance of the sympatho-adrenal system in the regulation of cardiac performance during dynamic exercise. A study was, therefore, designed to investigate the haemodynamic changes during supine leg exercise before and after β -adrenergic block with propranolol. The report on this investigation is presented in Chapter V.

An assessment of the changes in left ventricular performance during supine leg exercise, which has been used as the standard physiological stimulus, was also undertaken in the course of the study reported in Chapter V.

In Chapter I a summary of the present concepts (and some controversies) regarding the regulation of left ventricular performance is presented. Also included in this chapter is additional information relevant to the understanding of left ventricular function and the methods that may be used to assess this.

A detailed critique of the methods used is given in Chapter II.

Since it was not feasible to measure either end-diastolic fibre length or end-diastolic pressure in the left ventricle, the mean pulmonary wedge pressure has been used as an indirect estimate of left ventricular end-diastolic pressure and hence end-diastolic fibre length. It was felt necessary to determine the confidence with which the mean pulmonary wedge pressure could be used as an estimate of left ventricular end-diastolic pressure. To this end, therefore, another study was designed and the report on this is presented in Chapter III.

A brief comment on the statistical methods used is given in the appendix.

Since this thesis is being presented in two volumes, it was thought best, for ease of reference, to include all the tables and references in the companion volume.

CHAPTER I

THE CONTROL AND ASSESSMENT OF LEFT VENTRICULAR PERFORMANCE

A REVIEW

HISTORICAL NOTE:

A brief historical survey of the evolution of ideas about cardiovascular function, and their regulation is presented here. Only the important landmarks will be mentioned, the details being available in several recent publications. The present review is based mainly on the works of Willius and Keys (1941), Leake (1962) and Fishman and Richards (1964).

In the ancient Egyptian, Indian and Chinese literature, reference is found to the heart as being the centre of a system of distributing vessels and the association of pulse with cardiac action recognised. During the early Greek civilisation, while metaphysically orientated philosophical systems still defined the nature of reality, the heart was regarded as the seat of the soul. Alcmaeon of Croton (about 500 B.C.), the first Greek philosopher known to have practised dissection, distinguished the veins from arteries and taught that the seat of sensation was in the brain and not the heart as hitherto believed. The observation that after death some of the vessels arising from the heart were found to be empty, led them to be called "arteries". It was probably Plato (427 - 347 B.C.) who first recognised the heart as a pump that "transfers particles as from a fountain into the channels of the veins, and makes the stream of the veins flow through the body as through a conduit".

The first complete description of the heart, its valves, and the origin of great vessels, with amazing accuracy, is to be found in the Hippocratic document "On the heart", the authorship of which, though apocryphal, has been attributed to Philistion of Locroi. Aristotle (384 - 332 B.C.) is said to have named the aorta.

During the following few centuries a scheme of the cardiovascular system was developed by Erasistratus (310 - 250 B.C.) and Prexagorus (about 250 B.C.), and still later by Galen of Pergamon (131 - 201 A.D.). According to this scheme the left ventricle and arteries were believed to carry vital spirit and air (Erasistratus) or blood (Galen), the right ventricle and veins carrying blood which was believed to flow from the liver. Being in accord with the Hippocratic (460 - 375 B.C.) concept of humoral pathology and also the religious dogma of the time, this concept held sway throughout the Middle Ages. It was the Egyptian Ibn-an-Nafis (1210 - 1299 A.D.) who first described passage of blood across the lungs and refuted the Galenic concept of interventricular pores. Later, Michael Servetus (1511 - 1580 A.D.) and Realdus Columbus (1516 - 1580 A.D.) independently, but almost simultaneously, described the function of the lungs as that of gas exchange. The relationship between respiration and pulmonary circulation was established by Richard Lower (1631 - 1691 A.D.).

Although Leonardo da Vinci (1452 - 1519 A.D.) recognised the heart as a hollow muscle, it was Caesalpino (1519 - 1603 A.D.) who described the pumping action of the ventricles and emphasised the function of cardiac valves. It was, however, left to William Harvey (1578 - 1657 A.D.), who is said to have been influenced by his teacher Girolamo Fabrizzi (1537 - 1619 A.D.), to present a unified concept of the circulation and proof of the unidirectional flow of blood dependent upon the cyclical action of the heart. The only missing link in his thesis was the hitherto undemonstrated communication between arteries and veins. This gap was filled when Malpighi (1628 - 1694 A.D.) and

Leeuwenhoeck (1632 - 1723 A.D.) with the help of their microscopes demonstrated the capillaries. Harvey estimated the cardiac output in man to be 4 litres/min. In his Lumleian lecture (1616) he compared cardiac action to a water bellows. With the lay-out of "De motu cordis", Harvey also laid the foundations of a scientific method of enquiry, i.e. accurate observation and description of a phenomenon, tentative explanation of the observations, experimental evidence, and, lastly, a careful analysis of this evidence.

The anatomical nature of the heart as comprising of fibres, vessels and nerves was recognised by Niels Stensen (1638 - 1686 A.D.) and Richard Lower (1631 - 1691 A.D.) probably first described the inner and outer layers of the heart muscle. The course of the coronary vessels was described by Raymond Vieussens (1641 - 1718 A.D.).

Quantitative estimation of blood pressure in a variety of animals was first obtained by Stephen Hales (1677 - 1761 A.D.) using a water manometer. He also estimated left ventricular volume (160 c.c.) from a wax cast in a horse that died of exsanguination. Assuming complete emptying of the chamber, this gave an output of 6 litres/min. at a heart rate of 30/min. This rather low figure may have been due to the mode of death of the animal. Nevertheless he presented a broad concept of blood pressure and flow as also velocity of flow backed by quantitative measurements of each. He also showed the variation in blood pressure with heart beat and respiration and its low level in veins. The mercury manometer was invented by Jean Poiseuille (1799 - 1869 A.D.) and he used a rigid tube filled with a bicarbonate solution to obtain intravascular pressure measurements. He also defined the general

relationship that underlies our present day concept of blood flow and vascular resistance. The currently used sphygmomanometer in clinical work was developed by Riva-Rocci (1863 - 1937 A.D.).

During this time, important advances were also made in respiratory physiology when Cavendish (1765) differentiated a second gas from air (hydrogen) which he called "inflammable air"; and Joseph Priestley (1733 - 1804 A.D.) distinguished between "dephlogisticated air" (oxygen) and "phlogisticated air" (nitrogen). Later, Antoine Lavoisier (1743 - 1794 A.D.) described the principles of respiratory gas exchange and related respiration to combustion. Quantitative analysis of blood gases was first made by Heinrich Magnus (1802 - 1870 A.D.) and "Eduard Pfluger (1829 - 1910 A.D.) drew attention to tissue respiration.

The introduction of a kymograph and recording manometer by Carl Ludwig (1816 - 1895 A.D.) initiated the modern era of graphic registration of dynamic events thus providing a new dimension to biological research. The field of basic and applied physiological research has since progressed at a continuously accelerating pace.

Two Frenchmen, Auguste Chauveau (1827 - 1917 A.D.), a veterinary physician, and Jules Marey (1830 - 1904 A.D.), a Parisian physician, together recorded, for the first time, pressures from both the right and left side of the heart in a horse, using an air-filled rigid manometer. They recorded an average pressure of 27 and 129 mm.Hg. from the right and left ventricles respectively and noted that the left ventricular end-diastolic pressure was atmospheric.

The major contribution of Adolf Fick (1829 - 1901) was in the field of muscle physiology. He made precise quantitative measurements

and was the first to describe the length-tension relationship of muscular contraction. He brought mathematical principles to bear upon physiological phenomenon and formulated the well known "Fick principle" that has since been used for the estimation of cardiac output. This was also the first exposition of the indicator dilution principle and also laid the basis for the clearance techniques of regional flow estimation. In the absence of knowledge about the $A-VO_2$ difference in man, Fick assumed a figure from dogs and predicted a resting output in man of 4.6 litres/min. Experimental proof of the Fick Principle was provided by Zuntz and Hageman (1898) when they obtained right atrial blood of a horse at rest, exercise and during digestion.

The indicator dilution principle using foreign indicators was first used by Stewart (1897) when he measured changes in the conductivity of blood following continuous infusion of a salt solution. Henriques (1913) showed that measurements could be made just as accurately using a single bolus injection. Hamilton and his colleagues (1929 - 32) subsequently developed the method and placed it on a firm footing.

A young surgical intern, Werner Forssman (1929), working in Eberswald (Germany), while looking for a safe method for administration of drugs into the cardiac chambers in emergencies such as cardiac arrest, introduced a catheter into one of his forearm veins and advanced the tip into the right atrium. He repeated the procedure when no untoward effects were observed. Following his lead, Andre Cournand and his associates (1941) developed the technique of cardiac catheterisation in man. A mass of data from physiological and clinical studies has since flown from his laboratory. These studies established that the catheter

could be advanced into the right ventricle and pulmonary artery and left in situ for relatively long periods of time without any major complications.

Alongside of these developments other advances were being made in the understanding of cardiovascular function. Studies of pulse wave and pulse wave velocity were initiated by two German brothers, Ernest Weber (1795 - 1878), and Eduard Weber (1806 - 1871). Claude Bernard (1813 - 1878) discovered the vascular nerves and suggested the role of vasomotricity in the regulation of organ blood flow. The cardio-inhibitory action of the vagus was discovered by the Weber brothers and the accelerator nerves demonstrated by Bezold (1836 - 1868). The relationship between blood pressure and cardiac action was demonstrated by Etienne Marey (1830 - 1904) and the carotid sinus reflex by Johann Czermak (1828 - 1873). The unrivalled contributions of Otto Frank (1865 - 1944) and later Starling (1866 - 1927) in defining the intrinsic regulatory powers of the heart muscle now known as the "Frank-Starling Law" will be considered in detail in a later section. Frank's exposition of physical requirements in manometry is still unsurpassed. About this time also, the studies of Hermann Stannius (1808 - 1883), Walter Gaskell (1847 - 1914), Wilhelm His Jr. (1863 - 1934), and Albert Kent (1863 - 1945) were directed at the impulse conduction mechanism in the heart. The pioneering contributions of Augustus Waller (1856 - 1922), Willem Einthoven (1860 - 1927) and Thomas Lewis (1881 - 1945) in developing electrocardiography need also be mentioned.

The impact of these developments on modern thinking in relation to cardiovascular function is obvious. However, several significant advances have been made during the past 30 years or so. Some of these with a bearing on cardiac, in particular ventricular, function will be reviewed in the remainder of this chapter.

FUNCTION OF THE HEART:

The heart is the central organ which regulates the flow of blood to the tissues, and this appears to be its principle function. The successful use of extracorporeal circulation would suggest that the body does not recognise the heart as anything but a pump. Any other functions attributable to the heart have yet to be convincingly demonstrated. It should, however, be noted that the heart only regulates the total perfusion of the body, regional adjustments being under vasomotor control. In physical terms, the function of the heart is achieved by the transformation of potential energy derived from metabolic pathways into kinetic energy as the blood is propelled from the ventricles into the great vessels.

While in some invertebrates cardiac action is analogous to that of a rotary pump, in the mammalian circulation it functions more or less like a reciprocating pump (Brecher and Galletti, 1963). The wide ranging functional requirements of the cardiac pump may be summarised as follows (Br cher and Galletti, 1963):

1. Ability to vary flow rates between 3 to 30 l./min. and to pump against pressures up to 300 mm.Hg.
2. Even at maximum levels of stroke output the flow velocity must not exceed the tolerance limits for mechanical trauma (through either turbulence, friction or cavitation) of the formed elements in the blood (1 to 2 m./sec.).
3. The relationship between stroke volume and heart rate must not deviate much from an optimum determined by the elastic properties of the cardiac muscle, the time required for energy conversion processes and the lowest flow velocity compatible with the desired flow rate.

4. The valves must open easily at the onset of ventricular ejection and yet be competent to prevent regurgitation.

5. The regulation of the pumping action must be controlled by an elaborate system of feed-back mechanisms that integrate haemodynamic and metabolic data.

It is apparent, therefore, that a very elaborate system of controls must operate to regulate the function of the heart and bring it in line with the changing requirements of the body.

The ability of the heart to execute its normal function depends to a large extent on the functional competence of the ventricles, in particular of the left ventricle. This is not to say that the atria are devoid of any functional significance, but, as will become apparent in the course of this review, their main function is complementary to that of the ventricles. It is well known that ventricular fibrillation or standstill leads to the death of the organism while a fatal outcome does not, per se, follow the loss of atrial function.

Since the major aim of the present study was the assessment of changes in left ventricular function, the review has been largely confined to this aspect of cardiac function.

ANATOMICAL CONSIDERATIONS:

The functional anatomy of the ventricles is of fundamental importance in the understanding of their performance. A brief outline of the anatomical structure of the ventricles, therefore, follows:

In animals the ventricular muscle mass has been shown to comprise of separate bundles, the two bulbospiral and sinospiral muscles, each of which has a superficial and a deep component. Both originate from the cardiac skeleton (fibrous ring of the cardiac valves), the former

predominantly from the mitral valve ring (Robb and Robb, 1942). In the human heart identification of individual muscle bundles is difficult (Grant, 1953) so that the ventricles may be regarded as comprising of a superficial spiral group and a deep constrictor group of muscles (Rushmer et al, 1953) enveloping the chambers rather like a turban. The superficial spiral layer increases in size as it courses towards the apex in a clockwise direction, at which point the fibres take an approximately 90° turn, now spiralling towards the base in a counter-clockwise direction, and forming the trabeculae carnae and the papillary muscles. Between these two layers lies a circular set (Keith, 1918) which is most prominent over the left ventricle and probably represents the deep components of the spiral muscles (Rushmer et al, 1953).

The configuration of the two ventricular chambers accords well with their functional requirements. The left ventricle, free wall and septum, is a cylindrical cavity with a conoid segment at the apex (Rushmer and Thal, 1951), so that it has a relatively small surface area per unit of contained volume. In consonance with the Laplace Law the constrictor fibres (small radius) are well suited to raise intraventricular pressure to the relatively high levels normally demanded. On the other hand, the right ventricle resembles a crescentic pocket (the thin free wall against the interventricular septum) with a relatively large surface area per unit of contained volume, which permits large volume displacement per unit length of fibre shortening, but at a relatively low pressure. The changes in the configuration of the two ventricles that occur when a pressure load is imposed on the right side or a volume load on the left side also conform to these principles (Grant, 1953). Roentgenokymographic studies with and without metal

markers and cineangiographic studies have shown that ejection of blood by the left ventricle is accomplished by both lateral contraction and shortening of the longitudinal axis, but without any rotation, as would be expected from the orientation of various muscle bundles (Gauer, 1955; and Rushmer et al, 1953).

The ultrastructure of the cardiac muscle of mammals has been studied recently (Stenger and Spiro, 1961) and a striking similarity with skeletal muscle demonstrated. Briefly, cardiac muscle is composed of myofibrils (50 to 100 μ in length and 10 to 20 μ in diameter), which show a periodic band pattern under the light microscope. The sarcolemma, the cell membrane and intracellular structures are similar to those found in other muscles, except for the very large size of mitochondria in the cardiac muscle.

The fundamental structural and functional unit of contraction are the myofibrils made up of the myofilaments which are macromolecular complexes of contractile proteins, actin and myosin. The structure and orientation of these two proteins is the same in cardiac and skeletal muscle cells. The sarcomere length (between the two z lines) is intimately related to the overall muscle length and ranges normally between 1.5 and 2.2 μ . Although H-bands were not originally observed (Sonnenblick et al, 1963) more recent studies have demonstrated these bands in heart muscle as well (Huxley, 1964; Sonnenblick et al, 1964). Interdigitating bridges have been observed between the actin and myosin myofilaments in the region of the A bands. Recently, Huxley (1963) has also demonstrated such bridges in synthetic actin and myosin filaments and the polarity of these has been shown to be reversed at the two ends of each filament as would be expected according to the "sliding-filament"

principle of muscular contraction (Huxley and Niedergerke, 1954; and Huxley and Hanson, 1954) which has also been accepted as the cellular basis of cardiac contraction although some degree of actin filament folding has been suggested (Sonnenblick et al, 1963).

Left ventricular performance can be analysed in one of two ways depending upon whether the heart is considered to be a muscle that happens to function as a pump, or else as a pump that happens to be made of muscle. The former approach involves considerations of the mechanical behaviour and energetics of the heart muscle and the latter requires information about intracardiac pressures and blood flow together with their derivatives. Until recently attention had been mainly focussed on the second of these two approaches, but during the past few years, the importance of muscle mechanics in relation to cardiac function has been increasingly appreciated. Although differing in emphasis, both approaches are essentially complementary to the understanding of cardiac function as will be apparent in the course of this Chapter.

WHAT IS CONTRACTILITY?

Before proceeding to consider the regulation and assessment of left ventricular performance, a brief digression to examine the term "contractility" is desirable since it recurs frequently throughout the remainder of this report.

There is as yet no consensus as to the precise manner in which alterations in ventricular performance may be assessed in an intact organism. Ideally a quantitative measure of the rate at which a unit of heart muscle generates force would be desirable. Since this is not technically feasible various indirect estimates have been proposed. The term "myocardial contractility", most often used in this context, is

still wanting in a precise definition, chiefly because the physical basis of the term (as used) is incompletely understood. In the present study the following definition provided by Sarnoff and Mitchell (1962) has been accepted: "when, from any given end diastolic pressure or fibre length, the ventricle produces more external stroke work and more external stroke power (stroke work per systolic second) an increase in ventricular contractility is said to have taken place and vice versa. Implicit in this definition is an increased rate of development of tension when contractility increases. Specifically excluded is any increased work that may be done as the result of afterload from the same end diastolic length, since the rate of development of tension is not increased under such circumstances prior to the application of the after load".

When defined in this way changes in myocardial contractility are assessed by relating stroke work and/or stroke power to the end-diastolic pressure or fibre length. In this context, stroke work and/or stroke power provide an estimate of the external energy liberated by the ventricle. It is apparent, however, that either measurement severely underestimates the total energy liberated in a single beat (Chapter:II). Both the frictional losses and the energy used in heat production are ignored but it is assumed that these constitute a constant fraction. Again the kinetic work performed by the ventricle in imparting velocity to the blood ejected is also ignored. It has, however, been shown that kinetic work constitutes only a fraction of the total external work performed (4.9% at rest and 9.5% during exercise; Chapter:II).

As shown by Sarnoff and Berglund (1954) changes in myocardial contractility are best estimated from a family of "ventricular function curves" which are obtained by relating stepwise changes in the end-diastolic

pressure or fibre length with the corresponding changes in stroke work or stroke power. Each curve thus obtained defines a unique state of myocardial contractility. Myocardial contractility is said to have altered when a significant departure from the slope of such a curve is demonstrated. Further, an increase in myocardial contractility indicates a positive inotropic effect. It may be pointed out here that Sarnoff and Berglund (1954) arrived at this concept on an empirical basis. Nevertheless this concept of a "family of ventricular function curves" which define changes in myocardial contractility, has since been substantiated in the course of a systematic study undertaken by Sarnoff and his colleagues and also by reports from several other laboratories all over the world. The present day concepts regarding the mechanisms which regulate ventricular performance have to a large measure followed the clarification of the "Frank-Starling Law" (vide infra) offered by Sarnoff and Berglund (1954).

It should, however, be noted that criticisms have been levelled against this definition of myocardial contractility particularly by Rushmer et al (1963). However, even in their presentation of an analysis of left ventricular function in physical terms, Franklin, Van Citters and Rushmer (1962) do not provide a satisfactory alternative approach. Furthermore, their techniques of measurement cannot be applied in human studies at present.

The recent work of Siegel et al (1964), in which an attempt has been made to quantitate myocardial contractility, is of great interest. These authors have shown, with the help of experiments on isolated papillary muscles, intact dog hearts and human subjects, that the best

estimate of contractility is given by the index:

$$\frac{dp/dt}{llT}$$

where dp/dt = Maximum rate of pressure rise in ventricle
and llT = Integrated isometric tension.

Of particular importance is the fact that this index is independent of changes in the initial fibre length. These workers have also shown that changes in the end-diastolic fibre length do not affect V_{max} . (maximum velocity of shortening) while other known inotropic stimuli (e.g. noradrenaline, calcium and acetyl strophanthidine) and increasing frequency of stimulation increase V_{max} . with or without a change in PO (Isometric force). According to Podolsky (1961) " V_{max} . is an experimental measure of the absolute rate of the force generating chemical processes". It therefore follows that "true" inotropic stimuli should increase V_{max} . As already mentioned, Siegel, Sonnenblick, Judge and Wilson, (1964) claim that both V_{max} . and their "contractility index" $\frac{dp/dt}{llT}$ are independent of initial fibre length. These workers, therefore, suggest that "true" changes in contractility are produced by the inotropic stimuli which increase V_{max} . On the other hand, changes in the initial fibre length do not affect V_{max} . although PO is altered so that even while greater tension is produced this is not a "true" change in contractility.

The implications of this work are obviously far reaching and, if confirmed, may well lead to reorientation of some of the current concepts regarding ventricular function. However, it is only fair to point out that these workers do not refute the more traditional views but only state that their "contractility index" shows a better correlation with the physico-chemical definition of contractility which has been developed on

the basis of work on skeletal muscle.

With this preliminary background the current views on the regulation of ventricular performance are briefly outlined here.

THE REGULATION OF LEFT VENTRICULAR PERFORMANCE:

The relative importance of the various mechanisms which regulate left ventricular function is still a subject of some controversy although this is gradually dwindling. However, the principal mechanisms involved can be broadly grouped into two:

1. Intrinsic properties of the heart muscle.
2. ~~NE~~extrinsic mechanisms.

These will be considered individually.

1. Intrinsic Properties of the Heart Muscle:

One of the principal mechanisms which regulate left ventricular performance is what is commonly known as the "Frank-Starling Law".

Otto Frank (1895) devised an ingenious system to study "mechanical conditions under which cardiac motion takes place at will". He used frog hearts perfused with bovine or sheep's blood. His system enabled him to study both isometric and isotonic contractions of the ventricle and/or atrium. Frank concluded that the pressure developed by an isometrically contracting ventricle or atrium was a direct function of its diastolic length. He used intraventricular pressure as an index of the strength of contraction, a perfectly valid approximation in an isometrically contracting hollow organ. He also showed that the strength of contraction for a given diastolic volume was reproducible.

Starling (1915) came to a similar conclusion using a heart lung preparation. He measured changes in stroke volume at various inflow rates and at different aortic pressures. His often quoted conclusions were "the law of the heart is thus the same as the law of muscular tissue

generally, that the energy of contraction, however measured, is a function of the length of muscle fibre".

Starling, in his Linacre lecture (1915) stated, on the basis of evidence from his heart-lung preparations, that the circulatory adjustments during exercise involved increased venous return leading to dilatation of the heart which in turn produced a larger stroke volume. Several workers during the 1940s and 1950s vigorously contested the applicability of Starling's observations to the intact human circulation. Two pieces of evidence formed the background to this denial. Firstly, roentgenokymographic studies revealed that during exercise the size of the heart, instead of enlarging as Starling had predicted, either did not change or even diminished (Liljestrand et al, 1938; and Gauer, 1955). Secondly, following infusion of saline the right atrial pressures did not change while the cardiac output and usually the stroke volume were markedly affected (Stead and Warren, 1947). An interesting cross section of the views prevailing at the time were published in the form of a "Symposium on the Regulation of the Performance of the Heart" in *Physiological Reviews* (1955).

In 1952, Sarnoff and his colleagues initiated a series of experiments in dogs, the results of which demonstrated that the "Frank-Starling Law" is in fact valid even in the intact circulation. The chief contribution of these workers in this regard was the introduction of the concept that "a family of Starling Curves" defines adequately the performance characteristics of the heart (Sarnoff and Berglund, 1954; and Sarnoff and Mitchell, 1962). As mentioned earlier, these workers related changes in stroke work to the filling pressure of the ventricle over a wide range and then proceeded to study the effect of changing the

neuro-humoral background. They were then able to show that, when all other factors were held constant, ventricular stroke work was a direct function of the end-diastolic segment length or filling pressure, and that each such curve determined in a unique and predictable manner the performance characteristics of that ventricle. They have called this property of the heart muscle "heterometric autoregulation". Changes in performance or contractility were characterised by shift of the ventricle from one "function curve" to another with a different slope, hence the concept of a "family of ventricular function curves". Thus inotropic interventions "elevated" the curve and caused it to shift to the left (ordinate: stroke work; abscissa: filling pressure), and vice versa.

In the preceding few paragraphs it will have been noticed that the two terms "ventricular end-diastolic fibre length" and "end-diastolic pressure" have been used interchangeably. In fact both the "Frank-Starling Law" and Sarnoff's "ventricular function curves" are essentially related to end-diastolic fibre length. End-diastolic pressure is used in this context only as an indirect estimate of the end-diastolic fibre length. It has been shown that the pressure-volume curve of a ventricle both in man and in animals (Mitchell et al, 1960; Braunwald et al, 1960; and Aygen and Braunwald, 1962) has the shape rather like a rectangular hyperbola. Thus when stroke work is related to end-diastolic fibre length an almost linear relationship is found (Sarnoff and Mitchell, 1962) but when end-diastolic pressure is used in place of end-diastolic fibre length a curve that rises steeply initially but flattens off at higher levels of end-diastolic pressure is obtained (Sarnoff and Berglund, 1954). It must be pointed out that the only valid measurement of end-diastolic pressure in this context is the transmural or effective pressure

(Isaacs et al, 1954) and not the absolute pressure inside the ventricle. However, in the absence of changes in intrapleural or intrapericardial pressure, the absolute level of end-diastolic pressure should also allow an assessment of changes in ventricular performance.

Although Sarnoff's work was performed mostly in open chest dogs, evidence that similar properties characterise the function of the human heart has been gathered mainly by Braunwald and his colleagues. The findings of these workers have been recently presented in a summary form (Braunwald, 1965).

Most convincing proof that the intrinsic properties of the heart muscle constitute the fundamental mechanism which regulates ventricular function, has come recently from studies on the mechanics of cardiac muscle. Spiro and Sonnenblick, (1965), have studied changes in the ultrastructure of the cardiac muscle in relation to the active length-tension curve of an isolated papillary muscle from cats. These workers have shown that along the ascending limb of active tension the length of the I-band (not the actin filament) is directly proportional to the active tension developed by the muscle. The A-band length, on the other hand, remains constant (1.5μ) throughout the range of the length-tension curve. The peak of the active tension curve is reached at a sarcomere length of 2.2μ (resting sarcomere size 1.5 to 1.6μ). If the sarcomere be stretched beyond this length the active tension declines. However, the authors consider that the heart muscle probably never operates beyond the peak of the active tension curve.

The significance of these findings is obvious; they provide a structural basis for the "Frank-Starling Law" and, therefore,

further evidence in support of this regulatory mechanism.

Sonnenblick et al (1964) have related the passive pressure-volume curves from the dog and cat hearts to sarcomere length. The sarcomere length increases progressively as the filling pressure rises up to a sarcomere length of 2.2μ which is attained at a filling pressure of around 10 mm.Hg (upper limit of normal in intact animals). Beyond this, the filling pressure rises rapidly with only small increments in sarcomere length (cf. pressure-volume curve of the ventricle).

An additional piece of evidence in favour of the dominant role attributable to the "Frank-Starling Law" in the regulation of myocardial performance has been produced recently. It is well known that during exercise the overall size of the heart usually decreases (Liljestrand, et al, 1938; Braunwald et al, 1963; and Sonnenblick et al, 1965). As already pointed out this was, for a long time, held as evidence against the importance of the "Frank-Starling Law" in an intact organism. Sonnenblick et al (1965) have shown that when the heart of a subject at rest is paced at a rate that is attained during exercise, the end-diastolic and end-systolic volumes decrease and so does the stroke volume. However, during exercise at the same heart rate, these authors have observed that the end-diastolic volume of the ventricle increases from the resting paced size and concomitant with this the stroke volume also increases. It would, therefore, appear that the "Frank-Starling Law" operates even during exercise. Thus the mere fact that the stroke volume does not decrease during exercise is evidence that even in the presence of increased sympathetic activity during exercise, ventricular function is, in part, regulated by changes in end-diastolic fibre length.

It will be recalled that reference was made earlier to the

study reported by Siegel et al (1964) in which it has been shown that V_{max} . (Maximum velocity of shortening) is independent of initial fibre length. This has been interpreted as indicating that the "Frank-Starling Law" does not involve alterations in myocardial contractility. There is no doubt, however, that PO (Isometric force) is increased with increasing initial fibre length so that additional external work is performed by the muscle. It remains to be seen as to how the "Frank-Starling Law" will fit in with the present day concepts of muscle mechanics.

In addition to the "Frank-Starling Law" discussed above, two other intrinsic mechanisms which regulate ventricular performance have been described. These have been collectively termed "homeometric autoregulation" by Sarnoff and Mitchell (1962) as opposed to "Heterometric autoregulation" which is essentially synonymous with the "Frank-Starling Law".

The first of these two "homeometric" autoregulatory mechanisms is called the "Anrep effect". Anrep in 1912 observed, in a heart lung preparation, that when aortic resistance was increased the ventricular volume at first increased but subsequently declined. Similar observations were made by Stainsby et al (1956). Using an isolated perfused canine heart preparation, Sarnoff et al (1960) have shown this effect to be independent of coronary blood flow. A similar phenomenon does not accompany changes in stroke volume. Instead in the latter situation the left ventricular end-diastolic pressure increases with an increasing flow load (Sarnoff et al, 1960a).

Although the "Anrep effect" has been demonstrated in isolated heart preparations there does not appear to be a parallel phenomenon in the intact animal (Goodyer et al, 1962) or human heart (Ross and Braunwald, 1964). The importance of this mechanism (viz. increase in contractility following a pressure load) in the normal regulation of

of ventricular function, therefore, remains to be elucidated.

The second "homeometric" autoregulatory mechanism is the "Bowditch effect" (syn. "Treppe" or "Staircase" phenomenon). This defines the ability of an isolated heart to adapt to increasing frequency of contraction. The response is analogous to the "Anrep effect" being characterised by an initial increase in ventricular end-diastolic pressure which is followed by a decline in this pressure. By definition (with the stroke work held constant) this implies an increase in contractility. Sarnoff et al (1960) also observed this phenomenon in isolated perfused canine heart preparations.

The importance of the "Bowditch effect" in an intact organism remains to be clarified. In the isolated papillary muscle preparation Sonnenblick (1962) has shown that increasing frequency of stimulation results in an increase in V max. (maximum velocity of contraction) while PO (isometric force) is not significantly altered; a change that implies increased contractility (vide supra). On the other hand, in human subjects increasing the frequency of an artificially paced heart results in a reduction in stroke volume, stroke work and stroke power (Sonnenblick et al, 1965; Stein et al, 1966; and Benchimol and Liggett, 1966) and this is associated with a marked reduction in both end-diastolic and end-systolic volumes of the ventricle (Sonnenblick et al, 1965). Furthermore similar intervention does not alter the peak contractile force of the right ventricle in man (Sonnenblick et al, 1966). Thus the precise role of the "Bowditch effect" in the regulation of ventricular function remains to be defined. Sonnenblick (1962) suggests that a "velocity treppe" instead of a "force treppe" (as implied in the conventional definition of the "Bowditch effect")^{is} a more appropriate way of defining this phenomenon.

It appears, from what has been said above, that the only proven intrinsic mechanism which has a dominant role in the regulation of ventricular performance in man is the "Frank-Starling Law" or "heterometric autoregulation".

II. Extrinsic Mechanisms:

1. Most of the extrinsic mechanisms affecting ventricular performance exert their influence through the sympatho-adrenal system. The ventricular response to this effector system is briefly outlined here.

1. The neurogenic control of ventricular performance is principally mediated through the sympathetic innervation of the heart. With the introduction of selective adrenergic blocking drugs interest has been revived in the distinction of adrenergic receptors into the α and β types (Ahlquist, 1948). Both the chronotropic and inotropic effects on the heart are thought to be mediated entirely by the β -receptors (Ahlquist, 1948; and Chapter : V of this report).

Stimulation of the stellate ganglion in a canine preparation with controlled heart rate results in elevation of aortic systolic and diastolic pressures and a fall in filling pressure of the left ventricle, the resultant being a marked increase in contractility (Sarnoff et al, 1960b). With graded increased in the strength of stimulation a progressive and reproducible shift of the ventricular function curve demonstrates a stepwise increase in contractility (Sarnoff et al, 1960b). The rate of development of tension, the rate of fibre shortening and stroke power, increase while the duration of systole shortens.

Similar results have been reported by Anzola and Rushmer (1956).

Infusion of a variety of catecholamines also produce similar changes though quantitative differences have been observed (Goldberg et al, 1952; Cotten and Pincus, 1955; and Sarnoff et al, 1960). In man the

inotropic effects of both adrenaline and noradrenaline have also been confirmed (Goldberg et al, 1960). Nickerson (1964) has recently reviewed the role of adrenergic regulation in cardiac performance.

The marked inotropic effects of adrenergic stimulation have been demonstrated in an isolated papillary muscle preparation (Sonnenblick, 1962).

Further evidence regarding the role of the sympathoadrenal system in the regulation of ventricular function has been obtained from studies on animals with denervated hearts. Adrenergic blocking agents have been shown to adversely affect the haemodynamic response to any form of stress, e.g. exercise. A fuller discussion on this aspect of ventricular function is presented in Chapter V.

It has been suggested that sympathetic stimulation alters the distensibility characteristics of the myocardium, but Mitchell et al (1960) have presented evidence to the contrary.

The net effect of the sympatho-adrenal regulation of ventricular performance is to allow wide ranging adjustments in function without a serious encroachment upon the reserve intrinsic control mechanisms. Another protective effect is that by shortening the duration of systole in the presence of tachycardia, a relatively larger diastolic filling period for the coronary artery is made available.

The role of the vagus in the regulation of ventricular performance is less well understood. Sarnoff et al (1960b) did not find any significant changes in ventricular function on stimulation of the vagus. However, the importance of the vagus in the control of heart rate is well recognised (Glick and Braunwald, 1965).

Several reflex pathways are involved in the neurogenic control of

ventricular function. However, it is not within the scope of the present review to consider these in detail. Information on the subject can be obtained from the review of Folkow et al (1965).

Currently interest is being focussed on the role of the central nervous system in the regulation of cardiovascular function. Evidence is accumulating to suggest that the traditional concept of the vasomotor centre as a fairly well localised group of cells with a series connection with the rest of the nervous system, needs to be modified (Peiss, 1965). The trends of thought bearing on this and related problems have been recently published in the form of a symposium entitled "The Nervous Control of the Heart" (1965).

2. The role of the left atrium. It is now generally recognised that normal atrial activity is essential for the optimal working of the ventricle. In this regard the atrium functions as a booster pump which distends the end-diastolic left ventricle (normally) only fractionally but in the process enables it to liberate more energy from a larger volume (fibre length). The time in the cardiac cycle at which the atrial systole occurs is obviously important in this regard (Braunwald and Frahm, 1961 and Mitchell et al, 1963). This is best demonstrated in the presence of atrioventricular dissociation. By monitoring simultaneously the atrial and ventricular pressures in such a patient, Braunwald and Frahm (1961) were able to demonstrate that the ventricular contraction preceded by a properly timed atrial systole, produces a higher peak systolic pressure as compared to the cycles when this critical temporal relationship is not in evidence. Similar observations have also been made by Benchimol et al (1965) in man, and by Mitchell et al (1965) in dogs. Mitchell et al (1962), in an extensive series of experiments in dogs, have defined the

factors which influence atrial contribution to ventricular function.

3. Synchronicity of contraction. It has been suggested by Sarnoff and Mitchell (1962) that the degree of synchronicity between individual muscle fibres during contraction may significantly affect the performance of the ventricle. An absolutely synchronous contraction should result in greater work and power than would be attainable otherwise. They have reported that pacing from an intraventricular electrode causes the ventricle to perform less work as compared with an atrial site for pacing. Osadjan and Randall (1964) have shown that following stimulation of the left stellate ganglion, the time lag between the contraction of the first and last segments of the left ventricle is shortened, thus indicating increased synchronicity of contraction. This increased synchronicity during contraction may well be one mechanism of the inotropic effect of sympathetic stimulation.

ASSESSMENT OF LEFT VENTRICULAR PERFORMANCE:

It is obvious from what has been said so far, that the various mechanisms which regulate left ventricular performance are designed to enable this organ to meet wide ranging functional requirements. Any attempt at an assessment of left ventricular performance must, therefore, involve measurement of several related functions. Difficulties arise because of the interaction between these functions. In an isolated heart, or even in an intact animal, it is possible to control some of these variables while changes in a single variable are examined. However, for obvious reasons, this method cannot be applied in human investigations.

Earlier in this chapter it was stated that left ventricular performance could be assessed in one of two ways. If the ventricle is considered to be a pump which happens to be made of muscle, various

haemodynamic variables will need to be measured. Alternatively, if the ventricle is looked upon as a muscle that happens to function as a pump, information with a bearing on muscle mechanics will be required. These two approaches are only distinctive in methodology but do not materially affect the conclusions. The essentially complementary results obtained by following either approach have been repeatedly pointed out in the previous section. Some discrepancies that have arisen at times may well be due to incomplete understanding of one or the other phenomenon, e.g. it has been pointed out that increasing initial length of the muscle does not alter V_{max} while PO increases. It may well be that changes in V_{max} alone do not define completely all "forms" of changes in contractility. On the other hand, the "Frank-Starling Law" may be a regulatory mechanism which does not involve changes in contractility as understood by muscle physiologists. According to the "Frank-Starling Law" changes in initial fibre length will increase the energy liberated but according to Sarnoff's "family of ventricular function curves" a change in contractility only occurs when the ventricle shifts from one curve to another. The subtle distinction between these two statements is that while the "Frank-Starling Law" determines the shape of each "ventricular function curve" a shift from a curve with one slope to another with a different slope (which implies an increase in contractility) is not dependent upon the "Frank-Starling Law". This is implied in the definition of contractility given by Sarnoff and Mitchell (1962) and quoted previously. Thus while the "Frank-Starling Law" is valid during each state or level of contractility it does not play any part in the alteration of this state or level of contractility. Thus

the distinction between what Sarnoff said and what Sonnenblick has found may well be due to what each of them has left unsaid (or not said loud enough). The author does not claim any originality for these views, they are implied in the statements made by their respective exponents. On the other hand, the distinction presented has been deliberately magnified in a provocative manner in the hope that this may help to clear up some of the semantic confusion that still surrounds the term "contractility".

Be that as it may, the important point is that both muscle physiologists and haemodynamicians have arrived at similar conclusions even though they have approached the problem from different viewpoints. This is reassuring since the distinction between the pump and its structure is artificial.

The present author has followed the more traditional approach in the assessment of left ventricular performance, viz. that of haemodynamics. From this viewpoint the following measurements would be required for an adequate assessment of left ventricular function. However, as will be apparent, only a few of these measurements can be obtained in human experiments and for most others only approximations to the ideal requirement are routinely possible.

1. Volume changes of the left ventricle: Information with respect of both end-diastolic and end-systolic volumes is desirable. The end-diastolic volume, related as it is to end-diastolic fibre length, determines the performance of the ventricle in accordance with the "Frank-Starling Law".

The precise significance of the end-systolic volume is not at present understood but inotropic drugs like isoproterenol cause a proportionally greater reduction in end-systolic than in end-diastolic

volume (Harrison et al, 1964).

If intracardiac pressure is also measured simultaneously with the estimation of volume a pressure-volume loop may be obtained. It is possible to measure both kinetic and pressure work per stroke from such a loop (Bunnell et al, 1965).

Sonnenblick et al (1965) have also been able to determine the force-velocity relationship in man by estimating instantaneous volume changes and relating these with the intraventricular pressure.

There are, at present, three methods which can be used for the estimation of the dimensional changes of the left ventricle in man.

1. Biplane Cineangiography provides a volume diagram of a complete cardiac cycle. Dodge et al (1962) and Bunnell et al (1965) have used this technique to assess some aspects of ventricular function in man. Chapman et al (1959) had earlier obtained similar measurements in dogs. There are, however, several limitations in the use of this technique for experimental purposes. Firstly, only a few cardiac cycles can be examined at any one time and repeated injections in the same subject are not possible. Secondly, injection of the contrast medium itself produces quite marked haemodynamic changes (Brown et al, 1965) which raises difficulties in the interpretation of the data. Furthermore there is, at present, a significant risk attached to the procedure which cannot be ignored in experimental work.

2. Use of metal markers. Silver-tantalum clips have been sutured on the outside wall of a ventricle at preselected sites (Braunwald et al, 1963). High speed cine-films then provide an estimate of the sequential volume changes during a cardiac cycle. In addition, angiograms may also be obtained. Since the markers can be left in situ

the technique has the advantage that repeated measurements can be obtained. However, a thoracotomy has to be performed in order to secure the markers and this, obviously, limits the use of the technique to patients undergoing cardiac surgery.

3. Use of indicator dilution techniques. Direct injection of an indicator into the left ventricle while sampling from the aorta gives an estimate of ventricular volume but the accuracy of this method is questionable (Swan and Beck, 1960), and therefore the practical value of this technique remains to be established.

In the absence of a suitable technique which can be used, in practice, to obtain repeated measurements of volume changes in the ventricle, various indirect estimates of end-diastolic volume have been used. Since end-diastolic volume is a function of the end-diastolic pressure (Aygen and Braunwald, 1962), the latter provides a suitable estimate of end-diastolic fibre length. However, measurement of end-diastolic pressure requires left ventricular catheterisation which again is not without attendant risks, more so if measurements over a prolonged period of time are desired. For this reason indirect estimates of end-diastolic pressure are used as a measure of end-diastolic fibre-length. These are either the mean left atrial or the mean pulmonary wedge pressure. Formal evidence showing that the mean pulmonary wedge pressure is a reasonably accurate estimate of left ventricular end-diastolic pressure is presented in Chapter III.

It is obvious that with these indirect estimates of end-diastolic volumes no information about dynamic volume changes can be obtained (vide supra).

2. Energy produced during ventricular contraction: The common physico-chemical denominator in muscular contraction is energy. The fraction of the total energy expressed in a mechanical form is tension which during isotonic contraction is converted into work. Therefore the work performed by the ventricle is the physical quantity that is measured. During contraction the total work done by the ventricle is the sum of pressure work and kinetic work (Chapter:II). Kinetic work can only be measured if the velocity at which the blood is ejected is known. However since kinetic work has been shown to be only a fraction of the total work (Chapman et al, 1959) it is generally ignored.

The quantity generally expressed as stroke work is only a fraction of the total energy produced, but is hopefully accepted as a measure of the total energy.

Again in practice only the time integral of the instantaneous changes in stroke work is measured.

However, in spite of the unsatisfactory estimate of total energy that is given by stroke work, the latter has proved to be a useful quantity for the assessment of ventricular performance.

Another physical measure used in this context is stroke power which is the rate at which work is done. It will be recalled that in the definition of "contractility" both quantities appear.

For the assessment of ventricular performance, therefore, changes in stroke work and/or stroke power are related to the end-diastolic fibre length or appropriate indirect estimate of this.

It should perhaps be mentioned in passing that specially adapted strain-gauge arches have been used to measure the tension developed by the ventricular muscle during contraction (Sonnenblick et al, 1966). The method can only be used at the time of a thoracotomy and is therefore of limited value.

3. Maximum rate of change of pressure in the left ventricle:

It has been suggested that the first derivative of the ventricular pressure pulse (dp/dt) reflects changes in myocardial contractility. The possible significance of this measurement was apparently known to Frank (1895). Several workers have recently reported on changes in this measurement (Reeves et al, 1960; and Gleason and Braunwald, 1962), and there appears to be a general agreement that changes in dp/dt reflect changes in myocardial contractility. The measurement can be obtained with relative ease, but for any meaningful interpretation the frequency-response characteristics of the manometer-recording system used need to be of a higher order than that used for ordinary pressure recording (Patel et al, 1965). Miniaturised catheter-tip transducers are the most suitable, perhaps, for obtaining this measurement.

As previously mentioned, Siegel et al (1964) have proposed a "contractility index" which is independent of end-diastolic fibre length and correlates predictably with changes in V_{max} . The index is expressed as a ratio of dp/dt and integrated isometric tension (IIT).

The only difficulty in obtaining measurements of dp/dt is that left ventricular catheterisation is essential.

4. Velocity of ejection of blood: A technique for the measurement of the velocity of blood flow in the aorta has been described by Fry et al (1956). There is not much factual information on the use of this technique. Difficulties in calibration and rather cumbersome data analysis involved render the technique unsuitable for routine use at present.

Further difficulties in the practical evaluation of left ventricular function in man stem from the fact that there is, as yet,

no absolute standard against which individual changes can be judged.

It, therefore, becomes necessary to relate any changes in the indices of left ventricular performances to a standard established for the patient under similar circumstances.

Furthermore, in order to obtain a "ventricular function curve" it is necessary to induce graded changes in one or the other variable, viz. filling pressure or stroke work. This can be done by one of the following procedures.

1. Graded levels of exercise is the most commonly used procedure. Thus if it is desired to assess the effect of any particular intervention on left ventricular performance, the investigation should be so designed that graded exercise at equivalent loads is performed both before and after the "test intervention".

2. Administration of short acting potent pharmacological agents like adrenaline or isoproterenol.

3. Infusion of saline etc. with graded increments of flow rate.

While it is realised that coronary blood flow and myocardial oxygen consumption have an important bearing on the evaluation of left ventricular performance, it was not feasible to make direct measurements of these in the course of the present investigations. The literature on the subject has not therefore been included in the preceding discussion. A review on the regulation of coronary blood flow has been published recently (Berne, 1964).

CHAPTER II

METHODS

The data in these studies were obtained from measurements of cardiac output and cardiopulmonary blood volume; central aortic, pulmonary and right atrial pressure pulses; heart rate; and arterial and mixed venous oxygen content. In one study (Chapter IV) systemic arterial blood gas tensions (PO_2 and PCO_2), pH, and blood sugar levels were also estimated. The central aortic pressure pulse was analysed in detail. A number of related functions were indirectly calculated from these basic variables by appropriate mathematical formulae. While the plan of investigation in the different studies was adapted to suit particular requirements, the methods in general were similar.

The studies were carried out in a specially equipped cardiac catheterisation laboratory in the Department of Medicine, Royal Infirmary of Edinburgh. Room temperature was controlled between $68^{\circ}F$ and $70^{\circ}F$, and the relative humidity varied between 45 and 60 per cent in different studies, but not more than 3 per cent in the course of a single investigation.

All subjects, except (for obvious reasons) those in acute left ventricular failure, were familiarised with the laboratory surroundings and the details of the procedure on the day before the actual study. The investigations were carried out in the post-absorptive state. All subjects were studied in the supine position and no sedation was employed.

Cardiac catheterisation was carried out under strict aseptic precautions. Throughout the procedure, an electrocardiogram (lead CR4) was continuously displayed on an oscilloscope. A brief description of the catheterisation procedure follows:

Technique of intracardiac and intravascular catheterisation

1. **Right heart catheterisation:** Specially designed quadruple lumen cardiac catheters were used for simultaneous and continuous recording of pressures from the right atrium, pulmonary artery and pulmonary wedge positions, and to enable frequent injection of indocyanine green dye for estimation of cardiac output. These catheters (United States Catheter & Instrument Corporation, Glen Falls, New York), made of woven dacron, were 125 cm. long and each lumen was a 5F size (internal diameter 0.86 mm.), while the overall size of the catheters was 10F (external diameter 3.33 mm.). One lumen opened as an end hole at the tip, while the side hole openings of the other three lumens were spaced 15 cm., 20 cm. and 35 cm. proximal to it. The pulmonary wedge pressure was recorded through the lumen opening at the tip, while the second and fourth lumen recorded the pulmonary artery and right atrial pressures respectively. Indocyanine green was injected into the pulmonary artery through the third lumen.

The cardiac catheter was introduced into one of the antecubital fossa veins, usually on the left side, after a cut down procedure under local analgesia with 2 per cent lignocaine hydrochloride. Further manipulation was carried out under fluoroscopic control while the electrocardiogram was continuously monitored. The catheter tip was usually wedged in one of the right lower lobe branches of the pulmonary artery, but no attempt was made to define the exact location of the catheter tip. Confirmation of the wedge position was made by a study of the pulse waveform and the fact that this was asynchronous with the simultaneously recorded pulmonary artery and aortic pressure pulses. Sampling from this site, whenever possible, obtained fully oxygenated blood.

2. Arterial catheterisation: A nylon catheter (Portland Plastics Ltd., Hythe, Kent) 55 cm. long (internal diameter 0.9 mm., external diameter 1.34 mm.) was introduced into the brachial artery, on one or both sides as desired, by a modified Seldinger technique (Seldinger, 1953). After local analgesia with 2 per cent lignocaine hydrochloride, a Riley needle (17 S.W.G.) was introduced percutaneously into the brachial artery. Once inside the vessel a fish wire (length 75 cm., diameter 0.8 mm.) was threaded through it. The Riley needle was then withdrawn leaving the fish wire inside the artery. Gentle pressure prevented extravasation of blood around the fish wire. The nylon catheter was then threaded over the fish wire and the wire itself removed subsequently. The catheter could now be connected by its luer fitting, either to a transducer via a tap assembly, or direct to a Waters X C 300 cuvette as desired (vide infra).

3. Left ventricular catheterisation: This was performed only when comparing simultaneously recorded pulmonary wedge and left ventricular end-diastolic pressures (Chapter III). A radio-opaque teflon catheter (United States Catheter and Instrument Corporation, Glen Falls, New York), 100 cm. long and a 5F size (internal diameter 0.86 mm.) was introduced percutaneously into one of the brachial arteries, preferably on the right side, by a procedure identical to that of arterial catheterisation described above. Once inside the artery the catheter was connected up so as to display the pressure pulse continuously. It was then advanced retrogradely into the left ventricle under fluoroscopic control while both the electrocardiogram and the pressure pulse were being monitored. The catheter was given a shallow advancing loop to avoid possible entry into the coronary ostia, or injury to the aortic valve leaflets. Entry into the left ventricle was

indicated by a change in the contour of the displayed pressure pulse and was heralded by a transient arrhythmia but normal sinus rhythm was soon restored.

At the end of the investigation a single stitch was put at the site of the venous cut down. This ultimately left only a barely visible scar. On the arterial side the catheters were withdrawn and haemostasis secured by local manual compression, usually for 10 to 15 minutes. No complications were encountered. Minor extravasation of blood from the site of arterial puncture was invariable but no major haematoma formation was noted. All patients tolerated the procedures well.

A critical appraisal of the laboratory techniques used for various measurements follows:

Measurement of cardiac output and cardiopulmonary blood volume

Of the several available methods for estimation of cardiac output in man only two have found general acceptance for routine use. These are based on the Fick and indicator dilution principles.

The principle adopted by Adolf Fick in 1870 for the measurement of cardiac output states that the rate of uptake of a reference material by an organ must equal the net rate at which this substance is removed from that organ by the blood flowing through it; all other pathways of removal being excluded. In practice this is expressed by the following universally employed equation:

$$Q = \frac{VO_2}{AO_2 - MVO_2}$$

where Q = Blood flow in unit time (l./min.)

VO₂ = Oxygen uptake during the same time (ml./min.)

AO₂ = Average systemic arterial oxygen content over the same time (ml./l.)

$$\text{MVO}_2 = \text{Average mixed venous oxygen content over the same time (ml./l.)}$$

Thus

$$\text{Cardiac Output (l./min.)} = \frac{\text{Oxygen uptake (ml./min.)}}{\text{Systemic arterial - mixed venous blood oxygen content different (ml./l.)}}$$

It is obvious that several assumptions must be made if the Fick principle is to be applied in practice for the measurement of cardiac output in man. Besides the technical errors in measurements, any deviation from these rather exacting conditions is likely to reduce the accuracy of the results. In brief, the following considerations are important:

1. Whereas theoretically the Fick principle is valid only for the measurement of instantaneous flow, in practice it is used to measure time averaged flow. Errors are, therefore, likely to arise if the rate of flow changes during the period of measurement (Visscher and Johnson, 1953). Thus the method is applicable only during a 'steady state', (Fishman et al., 1952; Donald et al., 1955) and cannot be used in changing states, such as exercise, until a new level of stability is achieved.

2. The rate of oxygen uptake, as measured from the expired air, must equal the rate of uptake of oxygen by the blood traversing the pulmonary capillaries during that time. This then requires that during the period of observation the gas composition of both the inspired and the alveolar gases should remain constant, the alveolar gas volume should not change significantly, no loss of oxygen should occur prior to the site of sampling (such as may occur in pulmonary tissue metabolism) and the rate of transfer of oxygen across the alveolo-capillary interface should be constant. These requirements re-emphasise the fact that the Fick principle is applicable only during conditions

of strict respiratory and circulatory stability. Furthermore, because of the cyclical changes in the alveolar gas volume with respiration, the expired gas collection must cover whole respiratory cycles. Although in normal subjects the loss of oxygen in pulmonary tissue metabolism is small, it seems unlikely to be so in certain pulmonary pathologies.

3. Since in practice estimation of the oxygen content of the systemic arterial blood is time averaged, the oxygen entering the blood should be completely and instantaneously mixed with it and the volume of blood in the pulmonary capillaries should be constant.

4. The oxygen content difference between the systemic arterial blood and the mixed venous blood as measured, must equal the average oxygen content difference over the period of measurement. There is good evidence that the oxygen content in the mixed venous blood, and to a smaller extent in the systemic arterial blood, shows cyclical variations (Shepherd and Wood, 1954; Wood et al, 1955) which, in all probability, are related to phasic respiratory changes. Thus for accuracy of results the blood should be collected continuously over the period of measurement, including only whole respiratory cycles. Considerations of possible phase difference between pulsatile blood flow and blood oxygen content would require volume sampling instead of time sampling (Stow, 1954). Although on theoretical grounds the error introduced would be particularly large during circulatory and respiratory "instability", such as during exercise, direct measurements of cardiac output by two independent techniques suggest a random variation in the phase difference so that the precision of measurement is not significantly affected (Taylor, 1966).

5. The technical precision of the laboratory methods used for blood and gas analysis is probably the most important limiting factor in the

accuracy and reliability of the Fick method. While absolute accuracy is very difficult to obtain, particularly throughout the likely range of measurements, the errors must be known and taken into account.

6. The Fick method in principle should estimate pulmonary blood flow, but the admixture of blood from bronchial and Thebessian shunts narrows the calculated systemic arterial and mixed venous oxygen content difference, thereby giving a higher value for the calculated cardiac output. To that extent, therefore, the Fick method in practice measures the output from the left ventricle. The results would obviously depend upon the degree of admixture from such shunts (Stow, 1954; Fritts and Cournand, 1958).

Thus several considerations limit the use of the Fick method in practice and the reasons for not adopting it in the present study were:

1. The method is not valid for measurement of cardiac output in any situations other than those of absolute circulatory and respiratory stability.

2. Repeated reliable measurements cannot be made over brief periods of time, e.g. every minute or even at alternate minutes as was desired during this study.

3. No estimate of "central" or "cardiopulmonary" blood volume is possible since the mean transit time is not estimated.

4. The method itself is cumbersome.

5. It is uncomfortable for the patient to be breathing into a spirometer for long periods of time, up to two hours or more, as desired during some parts of this study.

Because of these limitations the indicator-dilution method, based on principles of fluid dynamics first applied to a study of the circulation of blood by Stewart (1897) and subsequently further developed by Hamilton and his colleagues (1928 - 1932), has found increasing use in various laboratories. The eponym "Stewart-Hamilton method" is justified by the pioneering contributions of these two workers.

When an indicator is continuously added to a constantly flowing stream, its concentration reaches an equilibrium level downstream which is a measure of the flow rate. Alternatively, when a known quantity of the indicator is injected rapidly a time-concentration curve may be recorded downstream which is a function of volume flow. Theoretically, there is little to choose between the two methods, as the constant infusion method has been shown to be the integral of a time-concentration curve obtained from a single injection (Hamilton and Remington, 1947; Meier and Zierler, 1954). However, it is difficult to obtain a satisfactory plateau in the intact circulation and no satisfactory method for excluding the recirculation elements has been devised (Howard et al., 1953). Further, the single injection method is more suitable for rapid and repeated estimations of cardiac output. The development of continuously recording dichromatic densitometers has improved the accuracy and ease of measurement by this technique. The introduction of green dyes, such as indocyanine green, the spectral absorption of which is quite independent of the oxygen saturation of blood, has further reduced some of the likely sources of error. This technique has, therefore, been standardised in the laboratory of the Department of Medicine, Royal Infirmary of Edinburgh, to give rapid, repeated, accurate and reproducible measurements; and has been used in the present studies.

In an unbranched system of continuously flowing fluid the amount of an indicator leaving in time dt equals the product of its average concentration and the volume of fluid leaving the system in that time.

$$\begin{aligned}\text{Amount of indicator leaving in time } dt &= (\text{Volume per unit time} \times dt) \times (\text{Average concentration of indicator in that time}) \\ &= Q dt \times C(t)\end{aligned}$$

The sum of such instantaneous values will equal the total amount of the indicator injected since all of it must leave the system sooner or later.

$$\begin{aligned}I &= \sum_0^{\infty} Q dt \times C(t) \\ &= Q \sum_0^{\infty} C(t) dt\end{aligned}$$

where I = the total quantity of the indicator injected

Thus if I is known Q can be calculated

$$Q = \frac{I}{\sum_0^{\infty} C(t) dt}$$

In practice, the measurement of instantaneous dye concentrations is very difficult and time consuming. Estimations at half or even one second intervals are normally quite adequate.

The ideal situation in which these theoretical principles are in fact applicable (Zierler, 1962) requires that:

1. The system must be a closed one with a single inflow, or a single outflow channel, or somewhere within the system the flow through any one channel must mix with that in every other channel. The volume thus measured is that between the sites of injection and sampling, and in a multi-channel system includes all channels with a similar distribution of traversal times.

2. There must be "stationarity" of flow. This implies that the traversal time of indicator particles should not change with time so that the

sequence of particles leaving the system at any one time is the same as at any other similar space in time. This assumption is violated by the pulsatile nature of flow in real vascular systems. If, however, phasic, not necessarily regular, changes in the distribution of traversal times fluctuate rapidly about a central value and the periodicity of these changes is brief as compared to the duration of the time-concentration curve itself, the error introduced may not be important. Other non-phasic changes in the flow rate or volume of the system during the passage of the indicator will, however, introduce a varying degree of error. Thus the method is valid only during conditions of circulatory 'stability', but because of the short period of transcription of a dye curve, especially after a central injection of the indicator into the pulmonary artery or one of its branches and sampling from the root of the aorta, it is possible to make fairly accurate measurements and to pick up fairly rapid changes. Duplicate measurements of cardiac output during a steady level of exercise have been shown to agree closely (Taylor, 1966).

3. Adequate mixing must occur before the indicator is sampled. This means that the frequency distribution of traversal times of the indicator particles must be the same as that of all other particles in the system. Most indicators are either tagged to a fraction of the plasma or the red blood cells. The ratio between the traversal times of red blood cells and plasma has been estimated at 1.1 (Fries et al., 1949). In practice, the error introduced in calculating blood volume from estimates of the traversal time of either red blood cells or plasma is therefore small. However, if there is a net loss of plasma or the indicator, e.g. capillary exchange, estimations of flow and volume are likely to be inaccurate.

4. There should be no stagnant pools in the system if the method is used for the measurement of volume of the system. This condition, however, is of no importance for the measurement of flow rate alone.

5. There should be no recirculation of dye before the first passage has been completed. In practice, early recirculation from the coronary, thyroid and other channels does vitiate the shape of the recorded curve. There are two ways to deal with this. The recirculation may be taken into account and mathematically dealt with (Zierler, 1962). This is, however, both experimentally and analytically, a complicated and time-consuming procedure. Alternatively, the shape of the primary curve can be recovered since the decay of the dye concentration has been shown to be exponential (Kinsman et al., 1929; Hamilton et al., 1932). Logarithmic replot of dye concentrations from the downslope of a dye curve, against a linear time scale yields a straight line before recirculating elements appear. Extrapolation of this line to very small concentrations (to infinity theoretically) will identify the course of the primary curve. No satisfactory theoretical principles have been advanced to explain this phenomenon. In vitro studies with different models do not reveal an exponential decay of the time-concentration curve (Hamilton et al., 1932; Rossi et al., 1953) but the introduction of a mixing chamber seems to "smooth" the curve out and to impress upon it such an exponential form. In the intact circulation the left chambers of the heart are believed to perform this function. In the majority of instances in this study the recirculation elements appeared very late on the down slope of the dye curve, presumably because of the proximity of injection (pulmonary artery) and sampling sites (ascending aorta).

Some other mathematical expressions have been used to estimate flow from indicator-dilution curves but these have not been validated and in any case do not give estimates of mean transit time (Zierler, 1962).

6. The dye injection must be instantaneous. In practice, some finite time, however short, is required for even a sudden injection. This does not affect the calculation of volume flow but for the estimation of volume zero time should be taken as midway between the start and the completion of the injection (Marshall et al., 1958; Zierler, 1962).

7. The volume of the indicator injected must be very small in order not to significantly alter the volume flow of the system itself.

8. The injection site must be constant. High velocity injection through a freely floating catheter is likely to cause catheter recoil which would introduce errors, particularly in volume estimations.

In addition to these considerations which govern the practical applications of the indicator-dilution principle, the characteristics of the indicator itself and the detecting instruments used will influence the accuracy of the results and the ease with which they can be obtained.

Thus the indicator should satisfy the following conditions:

1. It should be non-toxic.
2. It should be water soluble and suitable for sterile intravenous injection.
3. Pharmacologically the indicator should be inactive, so as not to have any influence on the organism as a whole and in particular the cardio-respiratory system.
4. Precise estimation of the indicator concentration in whole blood or plasma should be possible and not susceptible to fluctuations in the composition of blood, in particular the oxygen content.

5. In the case of dyes their spectral absorption should be strong and the spectral transmission should stabilise instantaneously.

6. The indicator should not be metabolised during its first transit before detection, nor should it be sequestered during its first passage.

7. It should leave the system rapidly, and preferably completely, after first circulation so that no build up of background concentration occurs should repeated measurements be desired.

8. It should be non-staining so as to be cosmetically acceptable.

A recent advance in the practical application of the indicator-dilution technique has been the development of indocyanine green, a tricarbo-cyanine dye, by Fox et al. (1956). Indocyanine green has its peak absorption at 800 m μ , the isosbestic point where both oxyhaemoglobin and reduced haemoglobin have equal spectral transmission, so that detection is independent of variations in their concentration. The dye rapidly forms a complex with plasma albumin (Fox et al., 1957). The spectral absorption of indocyanine green is at a slightly higher wavelength in vivo than in vitro but its spectral transmission has been shown to stabilise rapidly without any overshoot (Edwards et al., 1960). It has no known pharmacologic effects in man and is completely non-toxic even in high doses. Although the safety limit has been arbitrarily set at 2 mg./kg. this can be raised to 5 mg./kg. (Fox and Wood, 1960). The dye is rapidly and almost completely removed by the liver in its very first circulation (Wheeler et al., 1958; Cherrick et al., 1960). It does not stain tissues even in very large doses. Varying pH, electrolyte concentration, plasma protein concentration, etc. do not affect the spectral transmission. However, a recent report suggests that

certain reducing agents like sodium bisulphite (used as a preservative in some preparations of Heparin) markedly reduces spectral transmission of this dye (Cobb, and Barnes, 1965).

Two other minor disadvantages of this dye are (i) instability in solution so that it has to be freshly made up before each study. (It is, however, quite stable in the dry form). (ii) High cost, 50 mg. of the dye cost £2.18.4d. in Britain, and this is sufficient for about 20 dye curves only.

The instruments needed for the transcription of dye curves comprise a detecting element, the cuvette densitometer, and a recorder. The following requirements determine the choice of such a system (Fox, 1962).

- (1) The cuvette densitometer should have maximum sensitivity for the spectral absorption of the dye used which, in the case of indocyanine green, is 800 mμ.
- (2) The sensitivity of the cuvette should be large for even small changes in the dye concentration or else adequate amplification should be possible.
- (3) The system should be insensitive to changes other than the dye concentration itself, such as flow rate, haemoglobin content, pH, PCO_2 , non-isotonic solutions, etc. This is achieved in dichromatic systems by balancing the output of one photocell by another which is insensitive to dye concentration but sensitive to other changes. Similarly, the output of the cell should be so adjustable as to take into consideration varying background dye concentration.
- (4) The dynamic response characteristics of the system should be adequate to provide faithful transcription of dye curves. The contour of a dye curve is determined by the volume rate of flow through the vascular system, the volume of the vascular bed between the injection and sampling sites, the

distribution of the long and short circulatory pathways through the system, and other less well understood factors (Rossi et al., 1953; Sheppard, 1954). Distortion of the curve by sampling-recording systems will change the shape and time relationships, though not the total area under the curve (Marshall et al., 1961) thus invalidating measurement of volume by this technique.

In most sampling systems blood flow is laminar. Factors that flatten the velocity profile in this laminar flow will reduce the degree of longitudinal dispersion. Where such dispersion exists the shorter the time required for the blood column to pass the detecting photocell, the less will be the resulting distortion. Thus the dimensions of the sampling tubes and the cuvette lumen, together with the rate of flow through them, influence to a large extent the dynamic response characteristics of the whole system, the electrical components having a negligible effect in comparison (Fox et al., 1957). Obvious limitations in achieving ideal hydraulic sampling systems are the minimum length of catheter for sampling from the desired site, the lumen size essential to obtain a satisfactory flow rate and the need to keep blood loss to the very minimum in order not to significantly alter the very parameter being measured. With these limiting factors in mind the highest possible linear velocity obtainable will minimise the distortion effects due to the hydraulic system (Rossi et al., 1953; Fox et al., 1957; Dow, 1956; Sherman, et al., 1959; Sheppard et al., 1959; Milnor and Jose, 1960; Marshall et al., 1961). A volume flow ratio (V/F) of 0.5 or less has been suggested by Rossi et al. (1953) to provide the best fidelity of recording. Sherman et al., (1959) worked out a 'figure of merit' given by $\frac{V}{2Q}$ (V = Volume in ml. from the catheter tip to the mid-point of the optical path in the cuvette and Q = flow rate in ml./sec.) which should be less than half the interpulse time, or the expected time of change of indicator concentration at the sampling

site (once per cardiac cycle). It is difficult to determine the amplitude ratio at various frequencies in this type of system since it is not possible to produce sine-wave changes in dye concentrations and theoretical considerations preclude mathematical analysis. On an empirical basis, however, an equation expressing the relation between the 90% response time (T_{90}) to a square wave impulse, and the frequency at which the amplitude is reduced to 80% of static amplitude (F_{80}) has been worked out (Fox et al., 1957) so that

$$T_{90} \times F_{80} = 29$$

(5) The response of the detecting-recording system to varying dye concentrations must be linear at least over the likely range to be encountered. The photocell, the galvanometer, and the writing arm of the recorder need to be considered in this regard.

(6) The flow rate of blood through the cuvette must be constant as the light transmission of whole blood varies with the flow rate (Wood, 1950). No satisfactory explanation for this phenomenon has been advanced but it is thought to be due to the concentration of cellular elements in the centre of the blood stream due to laminar flow (Wever, 1954).

(7) The whole injection-recording system should be compact, easy to handle and to sterilise for obvious practical advantages.

In addition to these considerations, the precision of estimation of the injectate and subsequent manual measurement of the dye curves will determine the accuracy of results.

The technique employed in the present study for the measurement of cardiac output was designed on the basis of these and other practical considerations. A detailed description of the apparatus and method used follows.



The dye injection and withdrawal assembly, built in this department, was mounted on a special trolley and designed for accuracy, compactness and mobility. The indocyanine green dye ('Cardiogreen'®), of Hynson, Westcott and Dunning, Inc., Baltimore, Maryland, U.S.A.) was injected by a special (two millilitre capacity) spring loaded syringe (held in a cradle) designed to hold the plunger in a preset maximum withdrawal position at rest. A screw top on the syringe allowed adjustment of the volume of injection which was then held constant throughout successive injections. For injection the plunger was driven by a pneumatically operated ram. Pressurised air was fed into the back compartment of the housing around the ram through a solenoid valve and rate of air flow regulated by a flow valve. Mounting air pressure in the housing forced the ram forwards, pushing the plunger of the syringe ahead. Injection was completed on 0.3 sec. and the excursion of the ram itself (2 cm.) detected by a microswitch and recorded on paper as a square wave deflection of the dye curve base line (Fig. 1). On completion of the stroke another valve fed pressurised air into the front compartment of the housing, thus forcing the ram back while pressure behind was released. Recoil of the spring caused the plunger of the syringe to withdraw at the speed of movement of the ram which was regulated by the rate of air inflow.

The injection syringe was connected by fine plastic tubing through a three-way tap to the patient and to a reservoir flask containing the dye solution, also mounted on the trolley. The whole system could be operated by a single control switch. Depressing the switch turned the three-way tap towards the patient and then opened the valve system to initiate a forward stroke of the ram. The dye was thus injected into the patient through one lumen of a quadruple lumen catheter, which opened into the main pulmonary

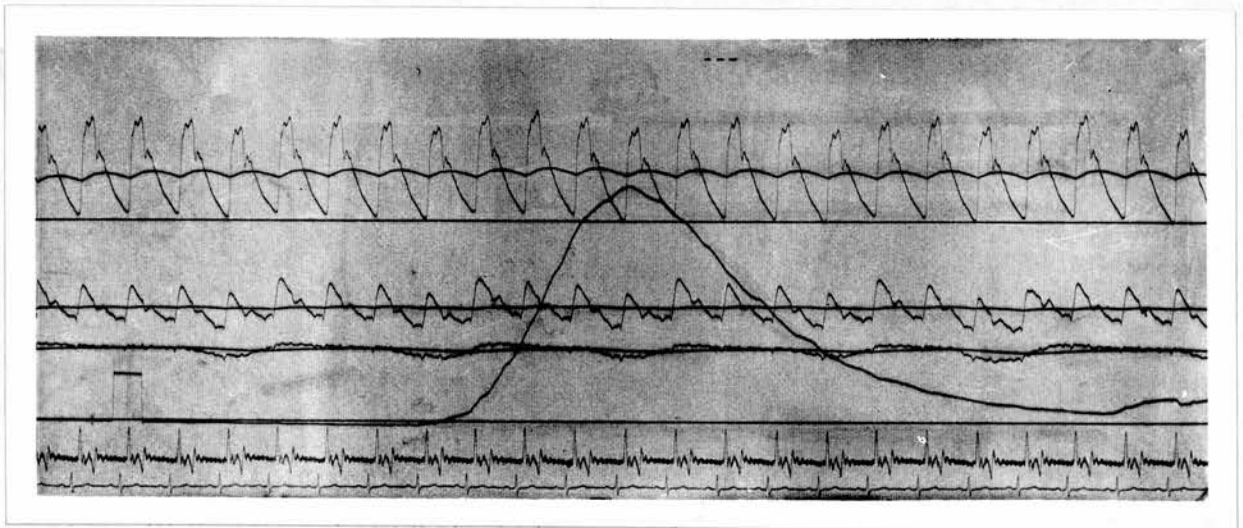


Figure 1

A specimen of the data in the analog form as obtained in one patient. Paper speed 3.4 cm./sec. Time markers in the background at intervals of 0.05 secs. First, second and third row: aortic, pulmonary artery and pulmonary wedge pressure pulses in that order. The electrically integrated mean runs across each pressure pulse. A dye curve is also shown and the square wave deflection of the dye baseline indicating the time and duration of injection is seen in the left hand corner. The output of a D-C differentiator and an electrocardiogram are seen in the bottom two rows.

artery, the exact site of injection being fixed by wedging the catheter. The catheter lumen was filled with dye from the same reservoir at the start of each study so that subsequent injections displaced an equivalent volume into the patient. On completion of the injection the tap turned to allow reloading of the syringe from the dye reservoir. The system was then ready for the next injection. This semi-automatic system, thus, allowed injection of a precise and constant volume of the dye each time. At the end of each study single (consecutive) injections were made into four preweighed dry flasks and the volume of dye estimated by reweighing them. Results were required to agree within 0.01 ml. Accurate measurement of the injection volume is absolutely essential, especially with the relatively small volume used in these studies. The injection volume varied between 1.200 and 1.600 ml. in different studies. The error in this measurement would therefore be $< 1\%$. The concentration of dye used was about 2 mg./ml. but knowledge of the exact concentration was not necessary in the method of calibration employed (vide infra).

The kinetic energy of the dye bolus thus injected invariably produced a small overshoot of approximately 0.5 to 1 cm. (as measured in clear fluid with a transparent nylon catheter of similar bore). As the volume of the dye injectate equalled 3 catheter lengths this would result in loss of dye equivalent to $< 0.2\%$ of the total injectate. This loss was, however, immaterial as the dye for volume estimation was taken through the same catheter and at the same injection pressures as used in the study, thus taking into account this overshoot.

When the interval between consecutive dye curves was more than 2 minutes, the catheter was flushed with an extra injection immediately prior to the definitive measurement so as to preclude any losses due to diffusion.

The dye blood mixture was sampled from the ascending aorta via a nylon catheter introduced into the brachial artery as already described. The catheter was connected in series to a Waters XC 300 cuvette, a tap assembly, and a Harvard dual withdrawal/infusion pump in that order.

The Waters XC 300 cuvette (Waters Corporation, Rochester, Minnesota, U.S.A.) has two cadmium selenide photocells, one with peak sensitivity about the maximum spectral absorption of indocyanine green (800 m μ) and the other with least sensitivity in this region, so as to compensate for changes in flow rate and optical density of blood other than those due to the dye alone. The characteristics of this cuvette as supplied by the manufacturers are as follows:

Lumen volume	0.01 ml.
Linearity range (dye concentration of blood)	48 mg./l.
Accuracy over entire range	$\pm 1\%$
Background dye concentration	36 mg./l.
Response time (67% of maximum)	0.06 sec.
Stability	1% of full scale

The cuvette-densitometer itself is of a fairly small size (1" x 3 $\frac{3}{4}$ ") and is connected to a control box by a long flexible lead.

The combined volume of the catheter-cuvette system (length 58 cm.) was 0.42 ml. At a flow rate of 38.3 ml./min. this gives a volume flow ratio of 0.66. Although this figure is higher than 0.5 as suggested by Milnor and Jose (1960) the calculations of these authors were based on peripheral sampling which itself introduces further dispersion, unlike the present study where dye blood mixture was sampled from the ascending aorta. Even when accepting their calculation this would introduce an error of $\leq 2\%$ and that

too only in abnormal circulatory states when recirculating indicator particles may appear high on the downslope of the curve. The 'figure of merit' (Sherman et al., 1959) works out to be 0.33 from this data and represents half the interpulse time at a heart rate of 90 per min.

The light source of the cuvette shining through the dye blood mixture withdrawn at a constant rate through the cuvette activates the photocells, the output of which (100 mV per mg./l. of dye) was fed through an amplifier in a control box to a N.E.P. ultraviolet recorder (Type 1185 New Electronic Products Ltd., London) utilising mirror galvanometers of 35 cm. focal length. The frequency response of the mirror galvanometers (Type BB 30) used was flat within 2% up to 20 c.p.s. The response of the complete dye curve recording system was linear to dye concentrations of 30 mg./l., which is more than three times the expected maximum of 7 mg./l. (Fig. 2). While the response of the photocell was completely linear with a constant 20 volts applied at an ambient temperature of 25°C, that of the galvanometer was linear ($\pm 2\%$) to 10 cm. on either side of zero. However, the distortion effect due to the light beam writing on a flat and not a curved surface, counter-balanced the galvanometer torque by adjusting the zero position of the light spot to one side of the centre of the arc. The peak deflection of all dye curves was so arranged as to be 15 cm. or less, so as to fall within the range of complete linearity (Kennelly, 1963) of the system. The dye base line was set 8 cm. from the edge of the paper.

The circuit of the original control box was modified to allow additional linkage with (a) an oscilloscope, thus permitting continuous display of recorded events, and (b) a cardiac output computer for continuous monitoring. The versatility of the control box was further improved by introducing a

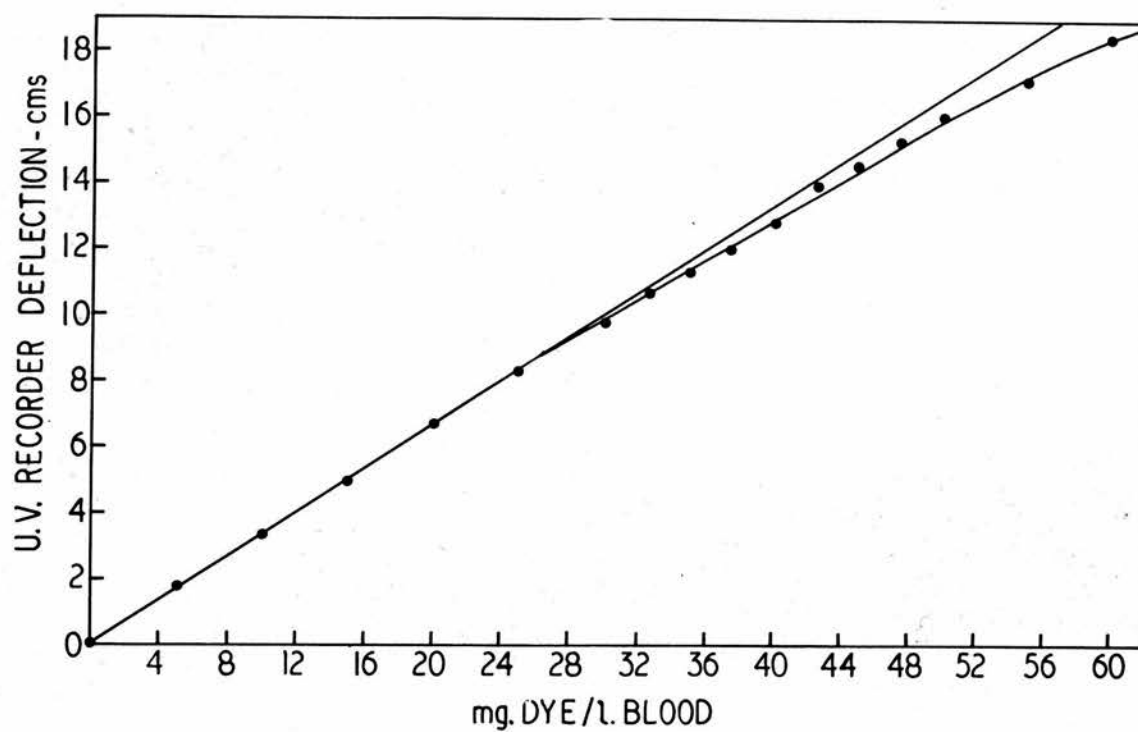


Figure 2

Calibration of the dye curve recording system. A linear response was obtained up to dye concentrations of 30 mg./l.

variable resistance sensitivity control switch allowing rapid adjustment of amplification as desired. The range of change in amplification thus possible assuming it to be maximum (100%) at 'sensitivity' 9 was 6.3%, 9.0%, 12.5%, 18.0%, 25.0%, 36.0%, 50.0% and 71.0% at sensitivity 1 to 8 in that order.

The Harvard dual withdrawal/infusion pump (model 600-910), employing a 1500 r.p.m. motor, had a speed selector allowing twelve different flow rates between 0.02 and 95.5 ml./min. The dye blood mixture was withdrawn into a 50 ml. syringe at a velocity of 90 cm./sec. and a constant flow rate of 38.3 ml./min. (speed 2 on the rate selector). Once the dye curve had been recorded the pump was reversed and the blood reinfused into the patient.

The tap assembly interposed between the cuvette-densitometer and the withdrawal syringe allowed flushing of the system with heparinised saline (from a central reservoir at a pressurehead of 300 mm.Hg) and withdrawal of blood samples if so desired, without having to disconnect any part of the system (Fig. 3). Of the five taps (Ole Dich, Denmark) in series, two were connected to separate drip systems regulated by flow valves, one being set to run at 10 ml./min. (Heparin 20 units/ml.) and the other at 0.5 ml./min. (Heparin 20 units/ml.). The side arm of the tap connecting the cuvette-densitometer allowed sampling of blood and that connecting the syringe could be turned to a waste connection if so desired. The central tap could be turned to a Statham P23Db pressure transducer for recording aortic pressures in between the dye curves. (This combined dye curve-aortic pressure recording assembly was not used in any of the present studies.) After reinfusion of blood at the end of each dye curve the system was flushed clear of blood by turning on the fast drip and then put onto the slow drip. The system was then ready for the next dye curve.

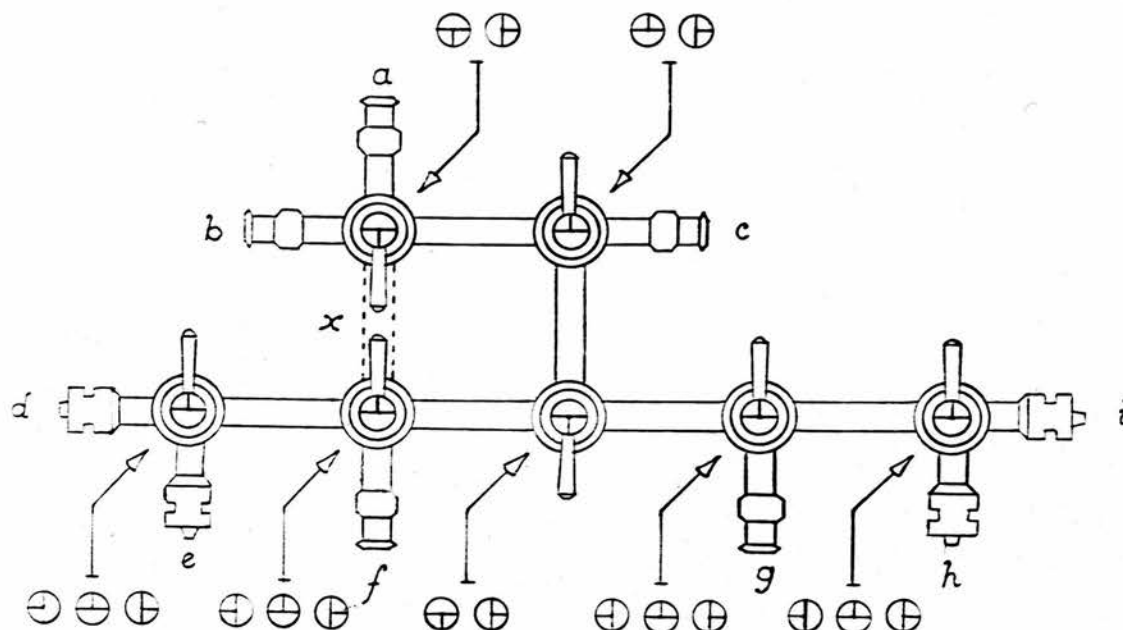


Figure 3

Schematic representation of the tap assembly used while recording dye curves. Arterial catheter was connected at i and withdrawal pump at d. Taps f and g provided connection for dripping heparinised saline at two different flow rates (see text). The side arm h was used for sampling arterial blood. A waste connection could be attached at e. The central bridge and the upper row of taps could be used for connection with a pressure recording system but this was not employed in the present studies.

In summary therefore at the start of recording a dye curve the taps were turned to allow withdrawal of blood and the pump started. The base line was adjusted by a technician working the dye curve control box and the recorder. Altering the intensity of the light source in the cuvette-densitometer allowed compensation for background dye concentration. This done, the dye injection was made while blood was being withdrawn at a constant rate. The operator in charge of the dye injection-sampling assembly followed the recorded events on the display oscilloscope. On completion of the dye curve transcription the pump was stopped and reversed to reinfuse the withdrawn blood into the patient, so that blood loss was kept to the very minimum. The whole system was then flushed with heparinised saline as described and held in readiness for the next curve.

At the start of each study one or more "trial curves" were recorded to adjust the sensitivity so that the peak of the dye curve was well within the linearity range of the system. In the majority of instances, dye curves were recorded at a paper speed of 3.4 cm./sec. with time markers at 0.05 sec. intervals (Fig. 1). In cases where, because of a large central blood volume the transit time of dye particles was prolonged, the paper speed was adjusted so that the curves could be conveniently lined up and measured. Once decided upon, the paper speed and sensitivity were not altered throughout the study.

The dye curves thus recorded on "Kodak Linagraph Direct Print" paper were measured manually. The curves were first lined up in free hand with a sharp point pencil to smooth out the pulsatile contour. Only curves with a steady base line were accepted. The appearance time (A.T.) was measured from the middle of the injection marker to the commencement of the

curve proper. Dye concentrations at half second intervals were then measured to the nearest mm. The downslope was plotted on semilog paper against a linear time scale. A straight line, drawn through at least five measured points, was used to extrapolate dye concentration to 1% of the peak value. The error in failing to plot to infinity could be expected to be < 1%. The dye curve area was then computed as the sum of these figures and the cardiac output calculated from the following formulae:

$$Q = \frac{I}{\sum_0^{\alpha} C(t) \times H \times S.A.} \times \frac{60}{(t)}$$

where Q = cardiac output (l./min./sq.m.)

I = injectate (mg.)

$\sum_0^{\alpha} C(t)$ = Sum of dye concentrations (cm.) at half second intervals (t)

H = Calibration factor (mg./l./cm.)

S.A. = surface area

The observer error in the manual measurement of a dye curve has been estimated as less than 1% (Taylor, 1966).

For calibration 120 ml. of arterial blood was drawn in dry syringes and run into a siliconed flask containing 0.5 ml. of Heparin (25,000 units/ml.) at the commencement of the study and stored at body temperature. The dye for calibration was taken from the same reservoir flask as used during the study. One ml. of the dye was accurately pipetted into a 25 ml. siliconed flask, and diluted with blood. The mixture was gently stirred to ensure mixing. One, two and three mls. of this dye-blood mixture were then pipetted into separate flasks and each further diluted to 25 ml. with blood. Dilutions of 1/625, 2/625 and 3/625 respectively were thus obtained. The mixtures were gently stirred to ensure mixing. Before calibration the cuvette was warmed by withdrawing through it saline at 37°C. To establish a base line a sample of non-dye blood

was then withdrawn. Next the dye mixtures were similarly withdrawn through the cuvette to record three step increases in dye concentration (Fig. 4). These were required to check within 5% of one another. The withdrawal rate in each instance was the same as used during the study. In some instances, the sensitivity had to be stepped down in order to be able to record all three steps. An appropriate correction factor was obtained from electric check signals (incorporated in the control box) which simulate the sensitivity changes.

If the concentration of the dye solution is C mg./ml., the volume used for each dilution (increments of $1/625$) is 1 ml., and the average height between calibration steps is L cm.; the calibration factor would then be:

$$\begin{aligned}\text{Calibration } H \text{ (mg./ml./cm.)} &= C \times \frac{1}{625} \times \frac{1}{L} \\ \text{or } H \text{ (mg./l./cm.)} &= C \times \frac{1}{625} \times \frac{1}{L} \times 1000 \\ &= \frac{C}{L} \times 1.6\end{aligned}$$

The formula for calculating cardiac output is (vide supra)

$$Q = \frac{I}{\sum_0^{\infty} C(t) dt \times H \times S.A.} \times \frac{60}{(t)}$$

I being the total amount of dye injected equals concentration (C) times the volume (V).

Substituting for H

$$Q = \frac{I \times V}{\sum_0^{\infty} C(t) dt \times \left(\frac{L}{1} \times 1.6\right) \times S.A.} \times \frac{60}{(t)} = \frac{V}{\sum_0^{\infty} C(t) dt \times \frac{1.6}{L} \times S.A.} \times \frac{60}{(t)}$$

If t (interval at which dye concentrations are measured) = 0.5 second

$$Q = \frac{V}{\sum_0^{\infty} C(t) dt \times \frac{1.6}{L} \times S.A.} \times \frac{60}{0.5} = \frac{120 V}{\sum_0^{\infty} C(t) dt \times \frac{1.6}{L} \times S.A.}$$

The errors in the estimation of cardiac output by this method have already been detailed and a composite assessment of these is given in Table 1.

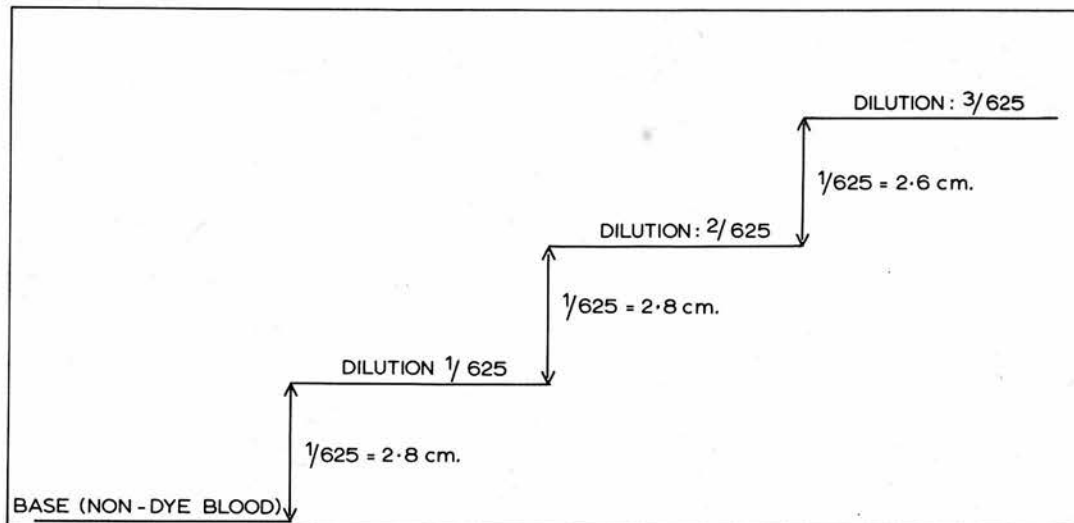


Figure 4

A representative dye curve calibration as obtained in one of the studies reported. Each step is a dilution increment of $1/625$. The average height of the three steps was used in the calculations. For details, see text.

Cardiopulmonary blood volume was also estimated from the dye curves. Theoretical validation of the Stewart-Hamilton method (Hamilton et al., 1932) for volume estimation has been provided by Meier and Zierler (1954) and Zierler (1962), while practical proof has come from Schlant et al. (1959). The basic assumptions involved have already been detailed (vide supra). The volume measured is that between the injection (pulmonary artery) and sampling (ascending aorta) sites, and includes all intervening territories with a similar distribution of traversal times.

That volume is the product of flow rate and the mean of all transit times is a fundamental fact,

$$\text{Thus } V = Q\bar{t}$$

V = Volume of the system

Q = Flow rate

\bar{t} = Mean of all transit times

If $h(t)$ is the fraction of indicator particles leaving the system in unit time then

$$h(t) = \frac{Qc(t)}{I} = \frac{C(t)}{\int_0^{\alpha} C(t) dt}$$

where $C(t)$ = concentration of indicator particles in that time

I = the quantity of indicator injected

Q = flow rate

Now the mean of the transit times of all indicator particles during the period of the 'curve proper' is $\int_0^{\alpha} t h(t) dt$

where t = Time between the first appearance of indicator particles and their final disappearance.

Substituting for $h(t)$

$$\text{Mean transit times of all indicator particles during the 'curve proper'} = \frac{\int_0^{\alpha} t C(t) dt}{\int_0^{\alpha} C(t) dt}$$

This equation does not take into consideration the time taken by the fastest indicator particles for their first appearance (A.T. = appearance time). Adding this to the equation

$$\text{Mean transit time } \bar{t} = \text{A.T.} + \frac{\sum_0^{\alpha} tC(t) dt}{\sum_0^{\alpha} C(t) dt}$$

The mean transit time thus calculated should take into account the time distortion produced by the sampling system used. With the sampling system used, this has been found to be 1.6 sec. and this figure was, therefore, subtracted from the result to arrive at the 'true' mean transit time of indicator particles. As used in this study, the equation, therefore, reads as:

$$V = \frac{Qt}{60}$$

where V = Volume (ml./sq.m.)

Q = Cardiac output (ml./min./sq.m.)

\bar{t} = Mean transit time (sec.)

Measurement of Intravascular and Intracardiac Pressures

In terms of pressure recording intraluminal pressure changes may be analysed into two components; an average mean pressure (Pa), and a superimposed alternating pressure (Pt). It is easy to record the average mean pressure alone even with a damped mercury or saline column. Accurate recording of the contour and amplitude of a pressure pulse curve, however, poses several problems. The pressure function of time consists of a number of harmonically related sinusoidal waves which determine the characteristic shape of a pressure pulse. A pressure pulse curve lends itself to Fourier analysis and it has been determined that such curves can be adequately described by the first six frequencies in the harmonic analysis (Porje, 1946; Hansen, 1949). Ideally, however, it would be desirable to have a recording system with a flat frequency response from zero to as high a frequency as possible.

The velocity, and hence phase relationships, of the various harmonics should also be constant to prevent distortion of the record. The early pressure transcribing devices were constructed without regard to their suitability for producing faithful records of pressure events until Frank (1903) expressed the theory and defined the requirements of such an apparatus. With slight modifications by Hansen (1949) these principles are still valid. Thus the various considerations that determine the adequacy of a pressure recording apparatus are as follows:

1. Accuracy of response at different frequencies: Considerations of amplitude and phase relationships between the response of the recording system and the input signal at different frequencies, define the frequency response characteristics of the system. Ideally, the amplitude of the record should vary in direct proportion to similar changes in the influencing signal over a wide range of different frequencies. On theoretical grounds as well as experimental evidence (Hansen, 1949; Noble, 1953), to achieve this the undamped natural frequency of the system should be higher in relation to the applied frequencies. The obvious solution would be to fix the undamped natural frequency at a very high level. This, in turn, entails considerable practical difficulties, the most important of which is the reduction in the sensitivity of the system. However, the degree of damping in the system has been shown to influence the range of frequencies within which amplitude distortion will not occur, e.g. at a damping of 0.6 ('critical damping' = 1) the deviation in amplitude is only $\pm 5\%$ when the relative frequency (ratio of applied frequency to undamped natural frequency) of the system varies between 0.8 and 0.85 (Hansen, 1949).

The phase difference angle has also similarly been shown to depend upon the relative frequency and the degree of damping of the system. Phase

distortion is less at lower values of relative frequency and lower degrees of damping. With a damping of 0.8, the relative phase difference has been shown to be practically constant for all frequencies up to the undamped natural frequency of the system (Hansen, 1949). Thus within the range of frequencies when amplitude distortion is minimal and the degree of damping is 0.6 all extrinsic influences will be recorded in correct form but with a certain displacement in time (which can be calculated). The degree of damping should therefore be between 0.6 and 0.8. With a damping of 0.7, less than $\pm 5\%$ distortion in amplitude and phase difference angle up to a relative frequency of about 0.6, has been demonstrated (Hansen, 1949). This degree of damping is also sufficient to prevent resonance and is, therefore, most suitable in practice.

The highest frequency likely to be encountered in physiological pressure recording could be taken as 5 c.p.s. (the atrial rate in atrial flutter) so that it should be possible to record, without distortion, frequencies up to 30 c.p.s. Appropriate calculations will then give the requisite undamped natural frequency as 50 c.p.s. when damping in the system is 0.7. Most of the time, however, the significant frequencies of a pressure pulse curve are likely to be far lower. In fact, Wood (1956) has shown that recording systems with a uniform dynamic response up to 6 to 10 c.p.s. are adequate for blood pressure recording in most physiological situations, but a more recent study (Patel et al., 1965) suggests that while these may be adequate in most instances, a uniform dynamic response up to 20 c.p.s. or more is desirable when information about the first and/or second derivatives of the aortic or ventricular pressure pulses is required.

2. Linearity of response to pressure changes: The amplitude of the recorded deflection must be a direct function of the magnitude of the

applied pressure and their ratio must be constant throughout the range of pressures likely to be recorded. It implies that the curve relating the amplitude ratio (recorded amplitude/true amplitude) to frequency should not be amplitude dependent. Thus the degree of non-linearity can be determined by a series of amplitude ratios versus frequency curves recorded at different driving wave amplitudes. Since no general statements can be made about non-linear recording systems these are best avoided (Fry, 1960).

3. Stability of response: This implies freedom from a drifting base-line as well as a drifting calibration or gain factor. Even frequent calibration checks, if these requirements are not fulfilled, would at best allow only an approximation of the true pressure changes. A plot of a series of calibration checks over a period of time would be an adequate test for stability. The lines of identity should be superimposable in a system with good stability. If the slopes of the lines are different, the gain of the system has drifted; while a disparity between their origins would suggest a drift on the base line (Fry, 1960).

4. Hysteresis: Ideally the response of the system should be instantaneous to any pressure step regardless of the manner in which this is applied. Hysteresis is said to exist if this condition is not satisfied. This can be tested by a series of square wave input signals of increasing and decreasing magnitude, the response being plotted against the magnitude of the input signal. The points should then fall on a straight line with inappreciable scatter or at best form a smooth and narrow loop. The latter would then comprise the hysteresis loop. The same property can also be examined by determining the response time to a square wave signal.

5. Responsiveness of the system to noise: The rapidly time-varying signals arising from sources unrelated to the physiological event being recorded are, in

general, termed noise. These could be mechanical, electrical or thermal. For obvious reasons, the noise level of the system should be such as not to interfere with the record. Thus the system should be insensitive to such extraneous influences as movement, acceleration, temperature change, etc.

6. Sensitivity of response: This requires that the system should be able to record accurately any minor but significant changes in the input signal. It is obvious, therefore, that considerations of linearity, response time, hysteresis and insensitivity to noise apart from the amplitude of the deflection have a bearing upon the sensitivity of the system. The amplitude itself can be varied by appropriate amplification as desired.

While the aforementioned characteristics determine the fidelity with which the response of the system will simulate the signal being measured, certain additional features need to be considered for the routine use and operational ease of such instruments (Sutterer and Wood, 1960). These are:

1. Usability with long flexible leads: This will obviously increase manoeuvrability and allow the use of such instruments in a variety of situations.
2. Imperviousness to electrolyte solutions: Since the sensing part of the system is likely to be filled with saline solutions, these should not alter the properties of the membrane itself.
3. Ease of clearing air bubbles: Apart from the likely hazards to the patient, even minute air bubbles introduce very marked damping and reduce the natural frequency of the system. It should therefore be readily possible to clear the system of any such air bubbles.
4. Sampling, flushing and injections: In most practical situations it is desirable to obtain samples of blood and/or inject pharmacologic agents through the same catheter from which the pressure is recorded. This should be possible with relative ease. Frequent flushing with an anticoagulant solution may also be desirable.

5. **Ease of calibration:** Calibration of the system should be easy since frequent checks during the process of recording are desirable to ensure the fidelity of recording.

6. **Ease of sterilisation:** To be available for ready use, it should be possible to sterilise the system quickly. This is particularly important because of the danger of transmitting infections, in particular, serum hepatitis.

Several pressure recording instruments have been developed over the years but considerations of their fidelity in recording narrows the choice to only a few. The older optical instruments, when properly adjusted, have excellent frequency-response characteristics, linearity and stability, but are difficult to handle and operate. Being very large they are space consuming and hard to fill. They are also very sensitive to movement. A continuous display of measurements cannot be obtained and photographic processing is inconvenient.

With the advent of electrical manometers with small pick-up heads connected by long flexible leads, the facility with which pressure records can be obtained has been greatly increased. They have, therefore, found ready acceptance in almost all laboratories. In principle, all existing pressure sensing devices are displacement recorders in which the displacement of a membrane is proportional to the applied pressure, and is measured by a transducer or a displacement gauge. The latter transforms mechanical displacement into an electric current, the voltage and time phase of the current being proportional to the displacement of the diaphragm and hence to the applied pressure. The output of the transducer is amplified if necessary and then recorded. The three major components of the system, viz: the transducer, amplifier and recorder, are arranged in series. Therefore, the amplitude ratio at a given frequency of the whole system will be equal to the product of the amplitude ratios

the principle that changes in the length of the wire produce proportional changes in its electrical resistance which, therefore, is a measure of the pressure applied. When such wires are used as one or more elements of a wheatstone bridge, changes in their electrical resistance unbalance the bridge thus altering the output current. Such strain gauge manometers are now being extensively used for pressure recording. They have been shown to have adequate dynamic properties and are free from significant hysteresis, baseline or calibration drift and relatively insensitive to temperature change (Fry et al., 1957).

In the present study, pressures were transduced through Statham P23Db (unbonded) strain gauge manometers coupled with carrier amplifiers (NEP type A 642) and NEP multichannel ultraviolet recorder (vide supra) using mirror galvanometers (Type BB 130). The frequency response of these galvanometers, as stated by the manufacturers, is within 95% of true fidelity up to 90 c.p.s.

The physical characteristics of the Statham P23Db pressure transducers are (Sutterer and Wood, 1960):

1. Displacement volume (ΔV) 0.035 cu.mm./100 mm.Hg
2. Volume elasticity coefficient 37×10^8 dyne.cm⁻⁵
3. Ambient pressure range -50 to +750 mm.Hg
4. Resonant frequency 225 c.p.s.
5. Calibration full scale Linear
6. Hysteresis % of ΔP < 1

The ultraviolet recorder used has considerable advantages over direct writing instruments which due to considerable inertia of the writing arms introduce significant damping. Furthermore, in such a multichannel system, the light beams can easily cross one another unlike direct writing recorders. The NEP recorder used could provide instant changes between the 21 paper speeds

of the individual components, and the phase lag of the over-all system will equal the sum of the phase lag of individual components. Ideally, the product of their amplitude ratios should equal unit and the sum of their phase differences should equal zero (Fry, 1960). These conditions being impossible to achieve in practice, a suitable compromise is to be aimed at (vide supra).

Electrical manometers based on three different physical principles have been introduced and will be considered in brief in this context:

1. Variable reactance of the inductive type.
2. Variable reactance of the capacitive type.
3. Variable resistance or strain gauges.

The inductance manometers (Wetterer, 1943; Motley et al., 1947) are based on the principle that the magnetic field of a coil changes when its metal core is either moved or compressed. The induction current thus set up is a measure of the pressure applied. The output of these manometers is small and needs to be amplified. The dynamic response characteristics are inadequate. They show a significant hysteresis and are sensitive to temperature change (Fry et al., 1957).

The capacitance manometers, developed by Lilly et al. (1947) and Hansen (1949), measure changes in the capacity of a condenser when the distance between its two plates is altered by an extrinsic force such as pressure. These instruments have fairly suitable physical properties and adequate frequency response characteristics. They have a relatively large output but still require amplification. Their chief shortcoming is a significant degree of hysteresis. Besides, they are sensitive to temperature change and are susceptible to cable interference.

Resistance wire or strain gauge manometers have been developed for use in physiological pressure recording by Lambert and Wood (1947) and Wood and Sutterer (1955) amongst others. These are based on

possible (from 0.084 mm./sec. to 203.2 mm./sec.). A rotating mirror in the path of the optical beam writes longitudinal time markers at 0.05, 0.5, 2.5, 5.0 and 25.0 sec. intervals, synchronised with the appropriate paper speed.

The static and dynamic response characteristics of the various combinations of catheter-manometer systems as used for intraluminal pressure recording in the present study were individually determined by the method of transient responses (Hansen, 1949; Fry, 1960) using air filled balloons. Although only square wave responses are thus obtained the damping constant and frequency response characteristics can be calculated by appropriate mathematical formulae making use of the magnitude of overshoot and after vibrations (Fry, 1960).

Thus

$$1. \quad h = \frac{(\log \frac{x_2}{x_1})^2}{\pi^2 + (\log \frac{x_2}{x_1})^2}$$

where h = damping constant

$\frac{x_2}{x_1}$ = ratio of the amplitudes of any two successive excursions of the transient response.

$$2. \quad \omega_u = \frac{\omega_d}{\sqrt{1 - h^2}}$$

where ω_u = undamped natural frequency

ω_d = the damped natural frequency or the frequency of the after vibrations

$$3. \quad ra = \frac{1}{\sqrt{(1 - \beta^2)^2 + (2h\beta)^2}}$$

where ra = amplitude ratio ($\frac{\text{recorded amplitude}}{\text{true amplitude}}$)

$$\beta = \frac{\omega}{\omega_u} = \frac{\text{driving frequency}}{\text{undamped natural frequency}}$$

$$4. \quad \tan \theta = \frac{2h\beta}{1 - \beta^2}$$

where θ = phase difference angle

The results can be expressed in radians per second or cycles per second (c.p.s.) depending upon the unit in which the damped natural frequency is measured. The latter unit has been used in the present study.

This procedure, although indirect, is theoretically perfectly satisfactory for the assessment of the frequency response characteristics of pressure recording systems (Fry, 1960). An attempt was, however, also made to study the dynamic response characteristics directly with the help of a variable frequency sine-wave pump. Results obtained were highly unreliable and it was felt that the amplitude of the input signal itself was frequency dependant and since no direct measure of this was available, the tests were abandoned. The problem of obtaining a constant amplitude variable frequency sine-wave generator are well recognised (Hansen, 1949).

In order to determine, as far as possible, the precise fidelity of recording during the actual studies the tap assembly used (vide infra) in these studies to facilitate frequent calibration and flushing was also interposed between each catheter and the manometer-amplifier-galvanometer system. The catheters were kept bathed in saline maintained at 37°C during these tests. The results obtained are summarised in table 2.

The frequency response and phase lag at different driving frequencies for all three catheter manometer systems are shown in Figs. 5 and 6 and the linearity of response to step-wise changes in input pressure in Fig. 7.

It is obvious that the dynamic response characteristics of these systems leave much to be desired. Nevertheless, it should be pointed out that most conventional systems in use in various laboratories have a uniform amplitude response up to 8 to 15 cycles per second only (Patel et al., 1965). In spite of

FREQUENCY RESPONSE CHARACTERISTICS OF THE PRESSURE
RECORDING SYSTEM USING EACH OF THE THREE CATHETERS

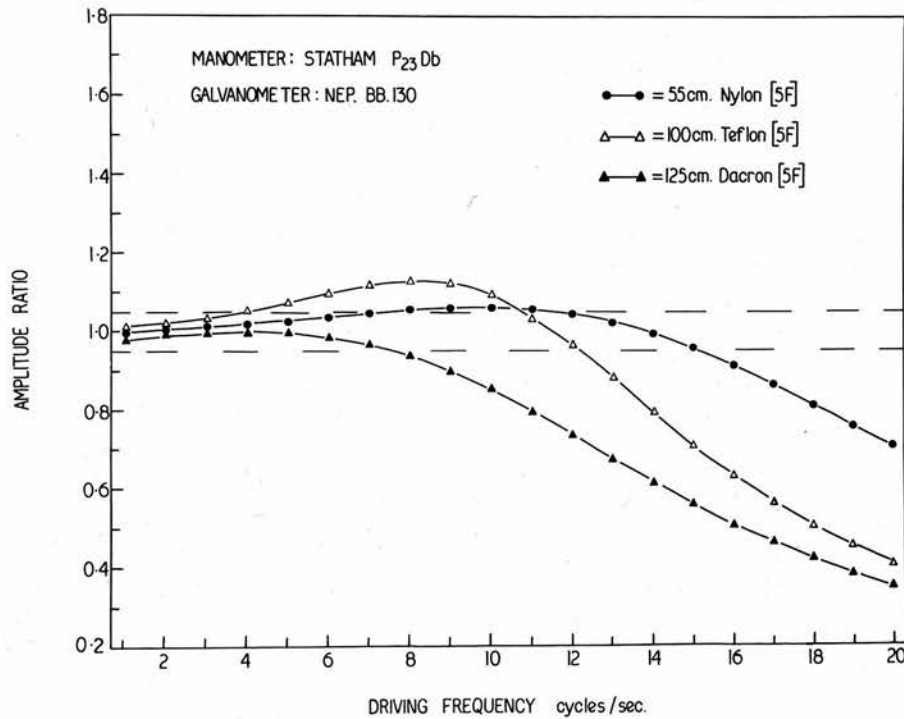


Figure 5

Frequency response characteristics of the pressure recording system using each of the three catheters. The interrupted lines indicate the 5% limits of variation in amplitude ratio.

PHASE LAG BETWEEN SINUSOIDAL FORCING FUNCTION AND THE RESPONSE OF THE
PRESSURE RECORDING SYSTEM USING EACH OF THE THREE CATHETERS

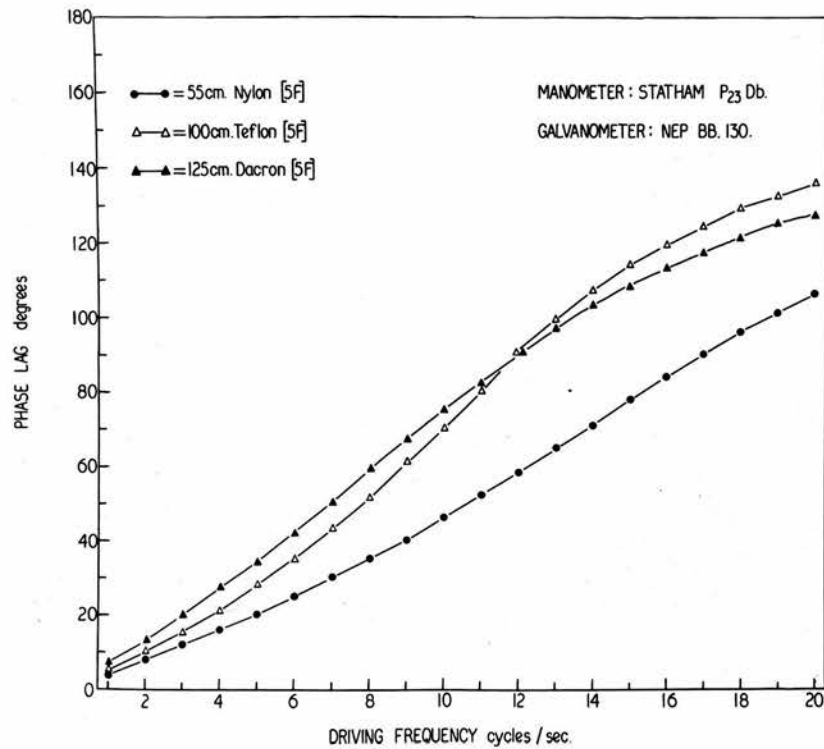


Figure 6

Phase lag between sinusoidal forcing function and the response of the pressure recording system using each of the three catheters.

RESPONSE OF THE CATHETER MANOMETER SYSTEM TO
STEPWISE CHANGE IN INPUT PRESSURE

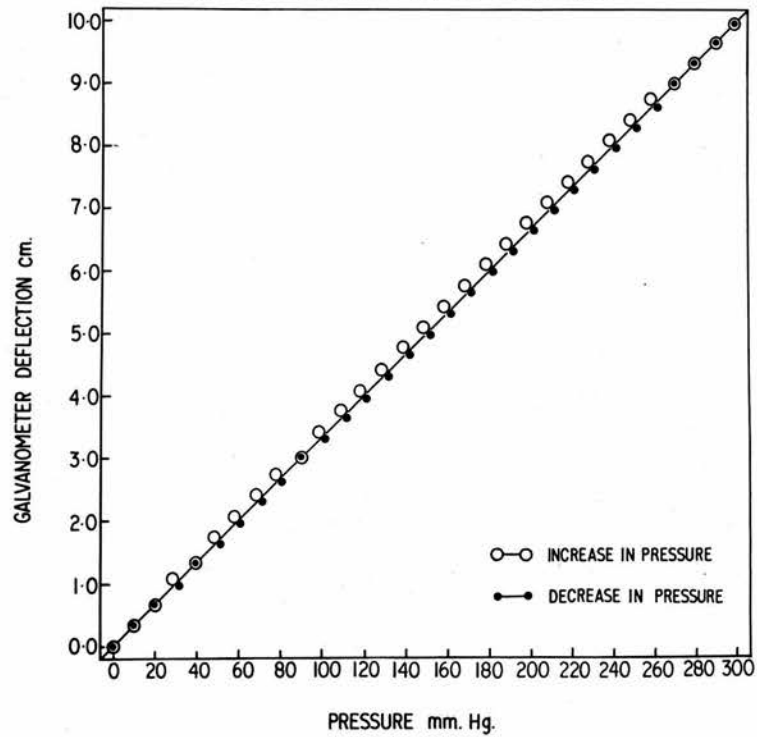


Figure 7

Response of the catheter manometer system to stepwise change in input pressure.

concerted efforts further improvements have not been possible so far. The limiting factors are obviously the catheter length, the volume elasticity characteristics of the material used (the catheters must be pliable), and the permissible lumen size of these catheters.

While admittedly an indwelling arterial needle would provide a system with much better fidelity of response, the effects of damping and resonance introduced by the length of the intervening vasculature between the heart and the site of arterial puncture would again be unpredictable. Besides, it is not practicable to leave an indwelling needle in position for up to 2 hours or more as required in some of the present experiments. The recent introduction of a miniature transducer attached to the tip of a catheter (Gauer and Giehuapp, 1950; Patel et al., 1965) certainly provides a much improved manometer but because of its relatively large size, it is not yet considered suitable for percutaneous arterial cannulation and certainly not for retrograde left ventricular catheterisation. An additional hazard in the prolonged use of this catheter would be clot formation. It is, however, hoped that a suitable manometer on these lines will be developed in the near future for such use.

Ideally, it would be required to test the dynamic response characteristics of the catheter-manometer systems each time before and after use. However, with an already heavy programme of investigation this was not considered practicable.

No attempt has been made to quantitate and correct for the likely errors, if any, resulting from the frequency response characteristics of these systems. As already pointed out, these are not of importance where mean pressure alone is measured. The combined calibration error and observer error have been estimated as $< \pm 2\%$.

The output of each manometer was so arranged as to provide a synchronous recording of both phasic and electrically integrated mean pressure except the channel recording right atrial pressures from which only the mean pressure was recorded.

All pressures in between the transcription of dye curves were recorded at a paper speed of 3.4 cm./sec. Immediately preceding or following a dye curve the aortic pressure pulses were recorded at a paper speed of 13.54 cm./sec. to provide an adequate spread of the pulse wave for detailed analysis (vide infra).

The venous (right heart) pressure recording systems were each calibrated against an open saline column mounted alongside the platform carrying the manometers. The arterial pressure recording manometer was calibrated against saline filled bottles pressurised by two calibrated Reckla aneroid manometers. For maximum recording precision with least electromechanical distortion the venous pressure calibrations were arranged to extend from zero to about 10 mm.Hg above the peak systolic pressure being recorded while on the arterial side these extended 5 to 10 mm.Hg on either side of the systolic and diastolic pressures being recorded. Frequent calibration checks were made to ensure recording precision. The sensitivity was so arranged as to obtain phasic pressure deflections of not less than 6 cm. while ensuring that these were always within the range of linearity of the galvanometers.

All pressures were referred to 10 cm. anterior to the back of the patient. The pressure transducers were mounted at this height so that no correction was necessary. However, in patients with left ventricular failure who had to be kept propped up, appropriate corrections were made.

For ease of calibration, flushing and sampling a tap assembly was introduced between the catheter and manometers as shown in Figs. 3 and 8. These taps (internal diameter 2 mm.) introduced a minimum of damping in the hydraulic system.

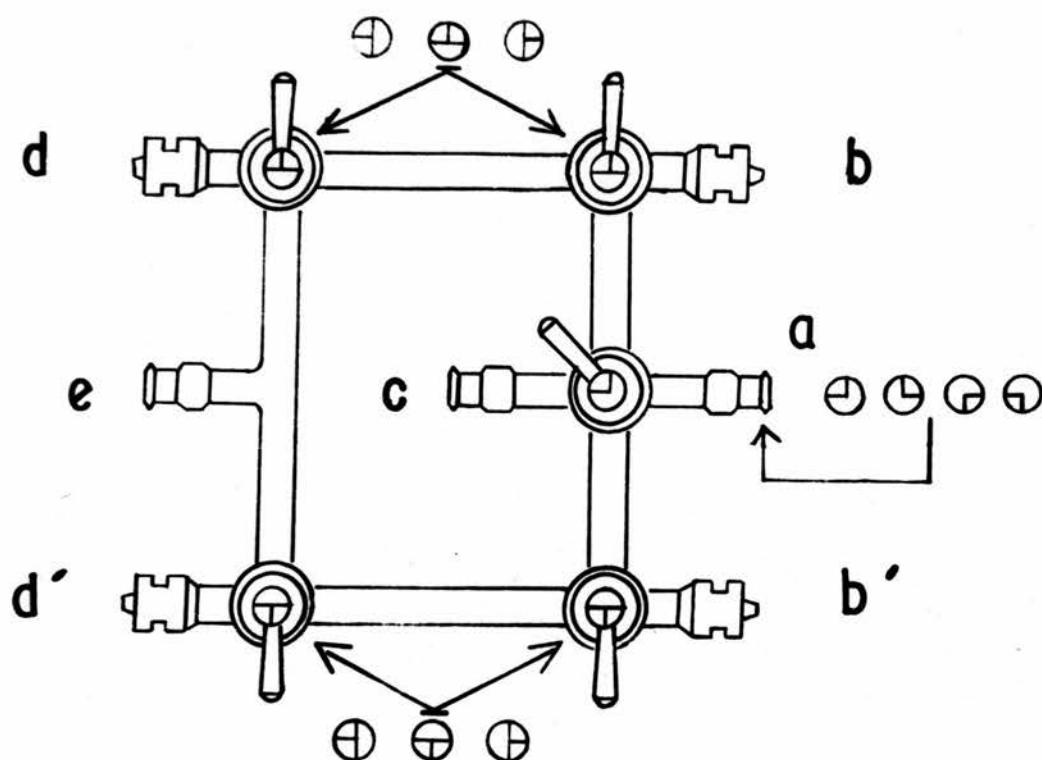


Figure 8

Schematic diagram of the tap assembly used while recording pressures from the pulmonary artery and wedge positions. A saline manometer for calibration was connected at a, while c provided the opening for registering atmospheric pressure. Transducers were connected at b and b' while the appropriate lumina of the catheter were connected at d and d'. A drip connection was attached at e.

Heparinised saline (20 units/ml. on arterial side and 4 units/ml. on venous side) stored in bottles and kept at body temperature, was used for flushing the catheters as a precaution against clotting. Between 15,000 and 20,000 units of heparin were thus given to any one patient but this did not prolong the clotting time significantly and no difficulty in securing haemostasis on completion of an investigation was usually encountered.

Sterilisation of the equipment used was carried out as follows. Pressure transducers were filled with a 1% solution of Benzalkonium chloride and left for at least 30 minutes. The cuvette oximeters were flushed with hydrogen peroxide and water after use and the connecting tubing siliconed with silicone ether after which they were filled with a 1% solution of Benzalkonium chloride. The tap assemblies were flushed clean with hydrogen peroxide and water before boiling. All connecting tubings through which blood was likely to pass were first siliconed with silicone ether and then autoclaved. The 55 cm. nylon catheter available in presterilised packs was disposable. The other catheters were left to drip with water overnight before being autoclaved.

Measurement of Blood Oxygen Content

To determine the oxygen content in samples of arterial and mixed venous blood, the percentage oxygen saturation and haemoglobin content (oxygen capacity) were measured. Samples of blood were withdrawn in tight fitting 10 ml. syringes containing a metal mixing ring. The average dead space in these syringes, filled with heparin (5,000 units/ml.), was 0.36 ml. In order to minimise dilution errors at least 4 ml. of blood were withdrawn for each sample. Care was taken to avoid trapping any air. Difficulties in this regard arose sometimes when sampling from the pulmonary artery, but the syringes were

immediately cleared of any trapped air and sealed with a hub cap. To ensure mixing the samples were placed on a revolving disc. All blood samples were analysed within 30 minutes of withdrawal.

Several methods are available for the estimation of blood oxygen content. Of these the principle ones are:

1. Manometric method of Van Slyke and Neill (1924)
2. Volumetric method of Haldane (Courtice and Douglas, 1947)

Both methods measure oxygen content directly as well as oxygen capacity. They give accurate and highly reproducible results. They are, however, time consuming and need expert supervision and for these reasons either method is unsuitable for analysis of a large number of samples as required in the present study.

3. Photometric methods. Several instruments based on the spectral transmission characteristics of haemoglobin are available (Wood et al., 1960). These can estimate oxygen saturation and/or capacity so that oxygen content can be derived. The principles have been described in detail by Zijlstra (1958), and Wood et al. (1960). Both transmission and reflection oximeters can be used. These are less cumbersome and more rapid than methods 1 and 2. Technical improvements now allow measurements to be made with the same precision as the method of Van Slyke and Neill (1924) except at low levels of oxygen saturation.

A further advance has been the introduction of continuously recording oximeters. The earlier ones could be used externally, such as ear piece oximeters or cuvette oximeters. More recently intracardiac fiber optic catheter oximeters utilising the principles of reflection oximetry have been introduced (Kapany and Silbertrust, 1964) but enough information about their practical

use is not available as yet. Calibration difficulties and relative large errors make the ear piece oximeter unsuitable for accurate measurements. Additional continuously sampling systems required for cuvette oximeters were impractical in the present study.

4. Indirect methods: Oxygen saturation can be derived when oxygen tension is known but the shape of the oxygen dissociation curve for blood introduces large errors at high oxygen tensions. In the present study oxygen saturation was measured by a Brinkman haemoreflector (Kipp and Sons, Co., Delft, Netherlands), and oxygen capacity in a Unicam spectrophotometer.

Oxygen saturation: The Brinkman haemoreflector used has been calibrated against the manometric method of Van Slyke and Neill (1924) using 87 blood samples (from different subjects) and tonometered at various oxygen tensions to obtain a wide range of oxygen saturations (Kennelly, 1963). The calibration thus obtained (Fig. 9a) was:

$$y = 14.9 + 2.12x - 0.00821x^2$$

where y = percentage saturation by the manometric method

$$x = 100 \left(\log \frac{\text{galvanometer deflection}}{10} - 0.5 \right)$$

Using this equation a linear relationship was obtained between the haemoreflector and manometric methods (Fig. 9b) and a nomogram constructed. Results were then read off the nomogram).

The 95% confidence limits allow an accuracy of 0.1% for oxygen saturations between 40 and 80% and only 1% at lower ranges. Concentration of indocyanine green up to 5 mg./l. have been shown not to affect the haemoreflector response (Kennelly, 1963).

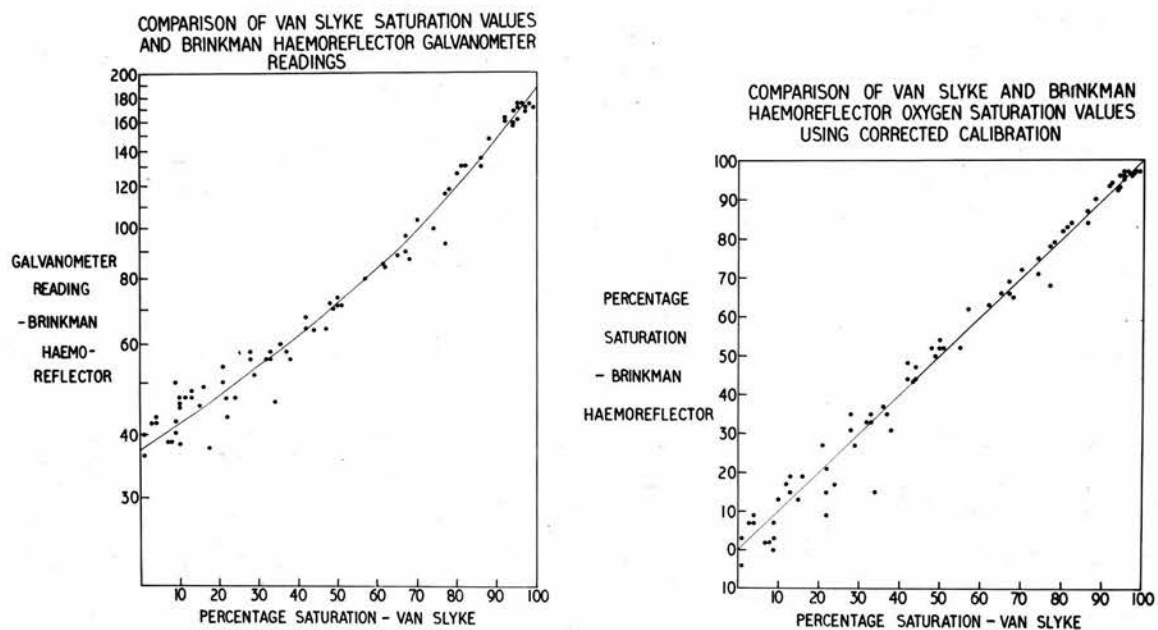


Figure 9
a and b

Comparison of the blood oxygen saturation values obtained by the Van Slyke method with the results obtained from the Brinkman haemoreflector. The left hand graph (a) shows the results of the direct comparison, and the right graph (b) the results when the haemoreflector readings were adjusted according to the formula given in the text.

The details of the procedure were the same as described by Zijlstra (1958). Briefly, 1 ml. syringes were loaded with 0.5 ml. of the diluent (2% sodium chloride, 0.3% sodium salicylate and 0.05% sodium cyanide) and filled with an equal quantity of blood. Separate syringes were used for each sample. Mixing was ensured by shaking for 15 seconds, after which duplicate galvanometer readings were taken and required to check within 0.2 cm.

Blood Oxygen Capacity: The Unicam spectrophotometer (Unicam SP 600) used was calibrated against the manometric method (Van Slyke and Neill, 1924) with the same 87 blood samples as used for calibrating the haemo-reflector (Fig. 10). Blood samples of 10 ml. were saturated by rolling in a siliconed flask with 100% oxygen for 4 minutes and duplicate measurements made by both methods. The regression equation of this comparison was:

$$y = 39.49x + 0.767$$

where y = oxygen carrying capacity by the manometric method

x = spectrophotometric optical density

The correlation coefficient of the two methods was 0.986 and the standard error of spectrophotometric estimate 0.012 (Kennelly, 1963).

In the present study, 40 cu.mm. of blood was taken in a haemoglobin pipette directly from the nozzle of the syringe containing the blood sample (after a few drops of blood had been expressed to clear the syringe nozzle of unmixed blood). This was then transferred to a test tube containing 10 ml. of 0.04% (V/V) freshly prepared solution of ammonia. Residual blood was thoroughly washed into the ammonia solution by repeated rinsing. The optical density of the solution was now determined by comparing with a blank 0.04% (V/V) solution of ammonia, using 10 mm. matched glass cells, at a wave length of 540 mμ. Measurements were made in triplicate for each sample.

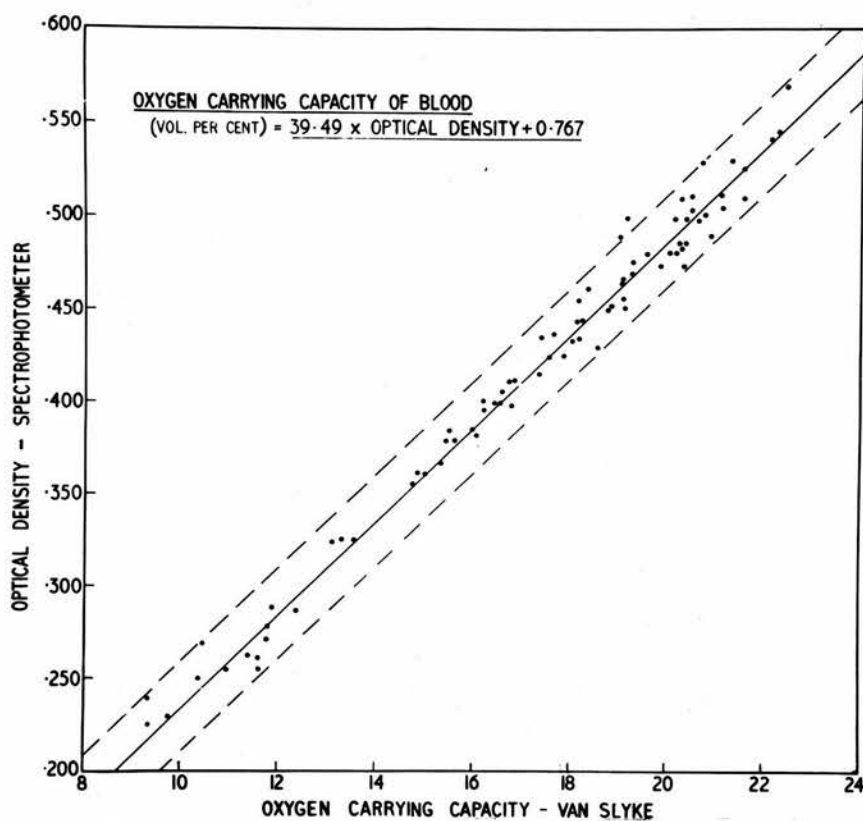


Figure 10

Graph showing the comparison of the values of blood oxygen capacity as obtained from the Unicam spectrophotometer with the results obtained by the Van Slyke method.

Measurement of blood gas tensions and pH

The introduction of electromanometric techniques for rapid and accurate measurement of blood gas tensions and pH, during the last 15 years, has led to their almost universal use. Recent developments in this field have been reviewed, amongst others, by Severinghaus (1962) and Bates and Christie (1965). It appears that, apart from technical considerations, there is little to choose between different available electrode systems. In the present study the blood gas tensions and pH were measured by the following methods:

1. Arterial blood oxygen tension was measured by the Clark polarographic cell (Bishop and Pincock, 1959) (Engineering Workshop, Department of Medicine, Queen Elizabeth Hospital, Birmingham).

Briefly the cell comprises a platinum (disc) cathode and a silver-wire reference anode. These are sealed in glass and bathed by an electrolyte solution of KCl which is separated from the test sample by a thin polyethylene membrane. The principle of the method is that the cathode emits electrons which reduce the oxygen diffusing across the membrane. The measured current is directly proportional to the oxygen available and therefore a measure of PO_2 .

In the present study, the electrode was calibrated with air after every 3 to 4 determinations. Nitrogen produced zero current. The electrode had been previously calibrated against the Scholander technique and a linear relationship found (Flenley et al., 1963). Blood tonometered with air gave a reading which was 95% of that obtained with air alone. This correction fraction ($\times 0.95$) was therefore applied to all readings. Measurements were carried out in duplicate and required to agree within 2 mm.Hg.

2. Arterial blood carbon dioxide tension was measured by a Severinghaus electrode (1958) (National Welding Instrument Co., Fremont Street, San Francisco). This consists of a glass electrode (cathode) and a silver-wire anode in a lucite housing. The electrolyte solution (0.01 M NaHCO_3 and 0.1 M NaCl) is separated from the test specimen by a teflon membrane permeable to carbon dioxide but not to electrolytes. Diffusion of carbon dioxide changes the pH of the electrolyte solution and the current produced is proportional to the H^+ ion concentration of the medium.

In the present study, the electrode was calibrated with two standard CO_2 mixtures before and after each study. Duplicate measurements were made for each blood sample.

3. Arterial blood pH was measured by a capillary electrode system (Electronic Instruments Ltd., Richmond, Surrey). This comprises a glass electrode (cathode) and a calomel anode. The response of the glass electrode is proportional to changes in the pH of a buffer solution surrounding it. The electrode was calibrated before each blood sample with a phosphate buffer (pH 7.416) which was in turn calibrated daily against Radiometer Co. precision buffers. Duplicate readings were made and required to agree within 0.004 units. Results were expressed to the nearest 0.01 unit.

The temperature of the water bath surrounding these electrodes was maintained at 38°C .

Estimation of arterial blood glucose concentration

This was performed by the enzymatic technique described by Huggett and Nixon (1957). The glucose in the protein-free filtrate of blood is oxidised by the addition of glucose oxidase. Hydrogen peroxide produced in the course of the reaction then oxidises the colourless O-Dianisidine, in the presence of peroxidase, to a chromogenic product. The intensity of the reddish-brown colour thus imparted to the solution is proportional to the glucose

concentration and is measured in a spectrophotometer. The range of normal values in this laboratory is 60 to 97 mg./100 ml.

A number of measurements, both direct and derived, were thus made in the course of the present investigations. A list of these, together with their rationale and limitations, follows:

1. Cardiac output (l./min./sq.m.) It is customary to relate the cardiac output to a standard total body surface area (one sq.m.), and designate the resulting measurement as "cardiac index". The justification for this has been called into question recently (Tanner, 1949; Reeves et al., 1961; Defares, 1965). However, in the absence of a better standard it was thought best to follow the conventional approach. There is some argument, admittedly semantic in nature, as to the appropriateness of the term "cardiac index". In the present studies, the term "cardiac output" has been used as synonymous with "cardiac index" since it is felt that the qualification used in the latter term is unnecessary and that the former describes appropriately the nature of the measurement, the unit of expression indicating whether or not corrections for total body surface area have been made.

A measure of reliability of the method used for the estimation of cardiac output is given by assessment of its reproducibility. The standard error of estimate from comparison of consecutive cardiac outputs in resting (supine) normal subjects when changes in the heart rate were one beat per minute or less, has been found to be 0.088 (Taylor, 1966). This indicates that, within a range of normality, consecutive cardiac outputs will differ by less than 6%. The percentage error would, however, be greater for lower outputs and vice versa. The results in the present study have been expressed to the nearest 10 ml.

2. Cardiopulmonary blood volume (ml./sq.m.) This was measured by calculating the mean transit time and cardiac output from dye curves as already described. The cardiopulmonary blood volume, thus measured, is the volume of all vascular territories between the pulmonary artery and the ascending aorta (vide supra) through which the indicator particles traverse and, therefore, includes the volume of the left atrium and left ventricle, together with other parallel channels, if any, which the indicator particles traverse. While it would be desirable to have precise information about the 'true' pulmonary blood volume (pulmonary artery to left atrium) no simple and satisfactory method is as yet available for such measurements in man (Fishman, 1966). Consecutive injections of indicator into the pulmonary artery and left atrium with sampling from the aorta is probably the best available method but involves transseptal catheterisation which was not considered justifiable or practicable in the present investigations.

The magnitude of the possible errors in the measurement of cardiopulmonary blood volume by the method employed have not been estimated. The results have been expressed to the nearest 10 ml.

3. Heart rate (beats/min.) The pulse frequency was calculated from the electrocardiogram at each minute. The actual measurement was made over a period of 30 seconds in each minute. The likely error by this method is therefore $< 4\%$, being less at higher heart rates.

The cycle length, both systolic and diastolic, were measured from the aortic pressure pulses recorded at a fast paper speed and used for pulse wave analysis (vide infra). A systematic error is introduced by the failure to take into account the duration of isovolumic contraction phase of the ventricle (aortic pressure pulses were examined) and this is further discussed later (vide infra) in this section. The systolic and diastolic minute durations are the product of the respective cycle lengths and the heart rate.

4. Stroke volume (ml./sq.m.) was calculated by dividing the cardiac output by the heart rate. As a derived measurement, therefore, it is susceptible to the compound errors of the primary measurements themselves.

5. Intravascular pressure (mm.Hg) Only the mean pulmonary artery, pulmonary wedge and right atrial pressures were measured. Artifacts and distortions, presumably due to the resonance characteristics of the pulmonary artery, are common on the pulse tracings from the pulmonary artery and so introduce an unpredictable error in the phasic pressure measurements, but these do not influence the mean pressure.

The mean pulmonary wedge pressure has been used in several clinical and experimental studies on the assumption that it reflects changes in the left atrium, pulmonary veins, and left ventricular end-diastolic pressure, but no direct proof of this has been forthcoming so far. A study designed to this end was therefore undertaken, since such an approximation is fundamental to the rest of the present investigations. This forms the subject matter of Chapter III. The results demonstrate the validity of this assumption.

The mean right atrial pressure is considered to reflect changes in the central venous pressure and therefore venous return. However, a severe limitation in such interpretation is the highly compliant nature of the venous system and the atria (Guyton, 1963).

Several measurements were made from the aortic pressure pulse (Fig. 17). Systolic, diastolic and mean aortic pressures were measured in each minute over a period of 20 seconds or more, but including only whole respiratory cycles. (This also applied to the pulmonary artery, pulmonary wedge and right atrial pressures.) The mean systolic ejection pressure, and mean

DIAGRAM ILLUSTRATING THE METHOD OF MEASUREMENT.

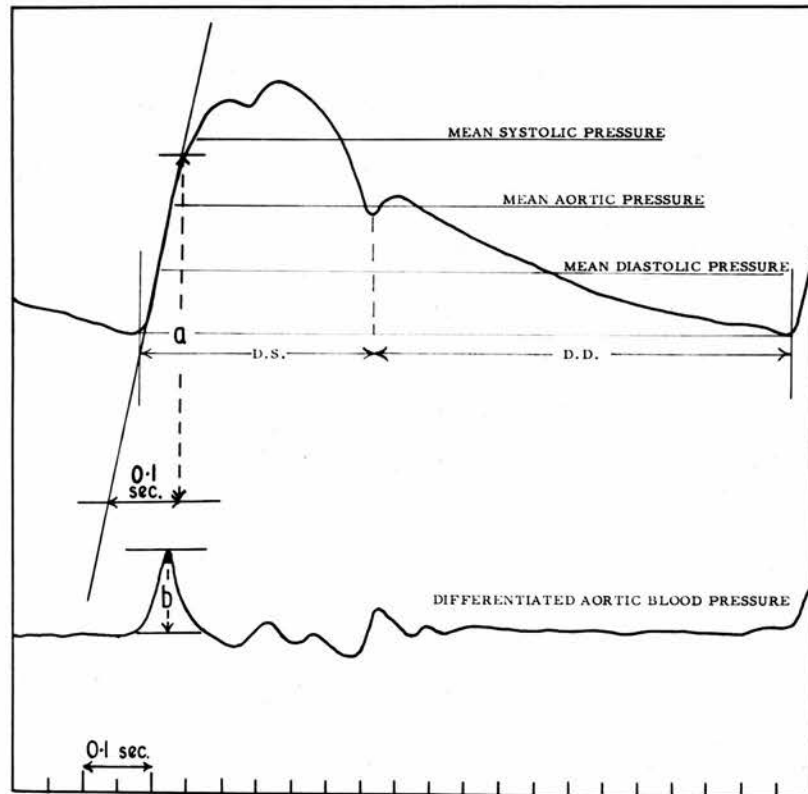


Figure 11

Diagrammatic representation of the method of analysis of aortic pressure pulses. The areas under both systolic and diastolic parts of the pulse wave were obtained by planimetric integration. The relationship of the various levels of pressure estimated is shown. The maximum rate of pressure rise was obtained from the tangent to the upstroke of the pulse wave. A D-C differentiator could also be used for this purpose.

aortic diastolic pressure were determined by planimetric integration of the 5 to 10 aortic pressure pulses recorded at a fast paper speed (13.54 cm./sec.) just before each dye curve. Care was taken to ensure that pulses over a whole respiratory cycle only were measured. Each pulse was planimetered at least twice or until the results agreed within 0.5 sq.cm. The mean systolic ejection pressure is taken to be a measure of the mean pressure generated by the left ventricle, during ~~systole~~ systole, while the mean aortic diastolic pressure is the pressure head at which most of the coronary filling occurs. Small errors may be introduced by failing to take into account the duration of isovolumic contraction of the left ventricle in the former instance and by including it in the latter calculation. A precise measure of such error is not available but on theoretical grounds this should be very small. Furthermore, the available evidence suggests that the isovolumic contraction period changes but marginally, if at all, over a wide range of pulse frequencies and therefore such errors would be systematic and unlikely to introduce a significant bias in the interpretation of changes from one state to another.

All pressure measurements have been expressed to the nearest mm.Hg. The observer errors in these measurements and those due to calibration have been liberally estimated as $\pm 2\%$. No attempt has, however, been made to define precisely the likely error resulting from the dynamic response characteristics of the pressure recording system. Such errors do not enter into the measurement of mean pressures but would certainly affect phasic pressure changes. The amplitude response of the catheter-manometer system used for aortic pressure measurement was within $\pm 5\%$ up to 15 c.p.s. (Fig. 4). This would allow 'accurate' reproduction (vide supra) of the pressure pulse

up to a pulse frequency of 90 per minute. For the most part in the present investigations, heart rates were below this level although exceptions were noted particularly during exercise.

The first derivative of the aortic pressure pulse was also measured (Fig. (7)). This has been expressed as the "maximum rate of pressure rise in the aorta" (mm.Hg/sec.). The significance of this measurement is not known. It seems likely that the first derivative of the aortic pressure pulse is a direct function of the first derivative of the left ventricular pressure pulse, although no proof of this is available. It was hoped that such proof could be obtained in the course of the present study, but several considerations, including the fact that the results would almost certainly be distorted by the limited dynamic response characteristics of the pressure recording systems used, led to the abandonment of these plans. The calculated results have been included in the data presented but because of the difficulties in precise interpretations not much reliance has been placed on them.

6. Vascular resistances ($\text{dyne} \cdot \text{sec} \cdot \text{cm}^{-5} \cdot \text{sq.m.}$) The calculation of vascular resistances provides an estimate of the number and size of a number of parallel arteriolar resistances that, together with the cardiac output, determine the arterial pressure (aortic or pulmonary). The number of these resistances is obviously a function of body size. The traditional calculation of such resistances by dividing the mean pressure (or mean pressure gradient across the vascular bed in question) by the cardiac output would suggest a lower resistance in a larger subject. A degree of uniformity is provided by referring the calculated vascular resistance to a unit body surface area as has been done in the present studies.

Thus

$$\text{Systemic Vascular Resistance} \quad \left(\frac{\text{dyne} \cdot \text{sec} \cdot \text{cm}^{-5}}{\text{sq.m.}} \right) = \frac{\text{Mean aortic pressure (mm.Hg)} \times 1.332 \times 60}{\text{Cardiac output (l./min./sq.m.)}}$$

and

$$\text{Pulmonary Vascular Resistance} \quad \left(\frac{\text{dyne} \cdot \text{sec} \cdot \text{cm}^{-5}}{\text{sq.m.}} \right) = \frac{\text{Mean P.A. pressure (mm.Hg)} - \text{Mean P.W. pressure (mm.Hg)} \times 1.332 \times 60}{\text{Cardiac output (l./min./sq.m.)}}$$

The systemic vascular resistance is over-estimated by failing to take into account the central venous pressure, but the latter is so small as compared to the mean aortic pressure and the error is less than that inherent in the measurements made.

The interpretation of the calculated pulmonary vascular resistance is severely limited in the absence of information about the changes in ventilation and intrapleural pressure (Fishman, 1963). It may be preferable to use the term "Pulmonary Flow Resistance" instead, thus avoiding any suggestion of changes in vasomotricity.

7. Oxygen uptake (ml./min./sq.m.) This was calculated as the product of the cardiac output and the A-V oxygen content difference. As in all such derived measurements the results are susceptible to the combined errors of the measurements actually made. However, a measure of the resulting error in the estimation of whole body oxygen uptake is provided by the comparison of simultaneously measured dye and Fick cardiac outputs (in a variety of normal and abnormal circulatory states) recently reported from this laboratory (Taylor, 1966), since the actual measurements of oxygen uptake and A-V oxygen content difference are made by the latter method. The results show that 95% of the 362 observations lie within $\pm 10\%$ of each other.

It may be pointed out that the assumptions underlying these calculations are only valid during constant flow.

8. Left ventricular work. If the ventricle is considered to be a pump, the 'effective' work done or energy expended is then given by the conventional equation:

$$W = [F \times D] + \left[\frac{MV^2}{2g} \right]$$

where W = work done

F = force

D = distance over which the force is active

M = mass moved

V = velocity at which the mass is moved

g = force of gravity

The second part on the right side of the equation represents the kinetic work. This fraction is difficult to calculate in the intact circulation. It has, however, been estimated that in dogs kinetic work of the left ventricle accounts for only 5% of the total external work during rest and 10% during exercise (Chapman et al., 1959). Routinely, therefore, only the first part of the equation is used and this gives the 'pressure work' of the heart. The equation then becomes

$$\begin{aligned} \text{Pressure work (W)} &= \text{Force} \times \text{Distance} \\ &= [\text{Pressure} \times \text{cross sectional area}] \times [\text{length of the blood column}] \\ &= \text{Pressure} \times \text{cross sectional area} \times \text{length of the blood column} \\ &= \text{Pressure} \times \text{stroke volume} \end{aligned}$$

$$\text{or } W = P \times V$$

or more appropriately when instantaneous pressure and volume changes are taken into account

$$W = \int_{T_0}^{T_1} P \times dv$$

In the absence of knowledge about instantaneous pressure and volume changes the results are calculated from the mean of these changes which introduces further inaccuracies. Chapman et al (1959) have shown that the error thus introduced is only of the order of 2.4% at rest and 4.7% during exercise.

Thus for the left ventricle:

$$\text{Stroke work (g.m./sq.m.)} = \left(\frac{\text{Mean S.E.P. (mm.Hg)}}{\text{Mean P.W. (mm.Hg)}} \right) \times \text{Stroke volume (ml./sq.m.)} \times 13.6$$

and

$$\text{Minute work (kg.m./min./sq.m.)} = \left(\frac{\text{Mean S.E.P. (mm.Hg)}}{\text{Mean P.W. (mm.Hg)}} \right) \times \frac{\text{Cardiac output (l./min./sq.m.)} \times 13.6}{1000}$$

where Mean S.E.P. = Mean systolic ejection pressure (vide supra)

Mean P.W.P. = Mean pulmonary wedge pressure

When Dexter et al (1951) first made use of these calculations the specific gravity of blood was also included in the formulae. This seems unnecessary since stroke volume is a measure of the distance traversed and not weight moved. In the present study left ventricular work is underestimated by 5.5% in comparison to those studies which have used Dexter's formula.

In addition to the limitations imposed on these measurements by failing to take into account the kinetic energy and by substituting mean changes for instantaneous changes, it must be pointed out that only a fraction of the total work performed by the ventricle is thus estimated. Frictional and inertial losses as well as energy expenditure in metabolic processes are ignored. It is hoped, but by no means proven, that such energy expenditure may be constant in any one state. Furthermore the basic presumption in making such measurements at all is that these provide

an estimate, however biased, of the energy expenditure by the ventricle. It has been pointed out that there are at least two conceivable situations where such approximation does not hold. Firstly if the ventricle were to contract isovolumetrically but the aortic valves did not open, the calculated work is zero ($v = 0$), or secondly if the ventricle were to eject when aortic pressure was zero a similar result would be obtained ($P = 0$). The first of these is the familiar situation during some premature contractions while the latter is only a theoretical possibility.

In spite of the inadequate nature of these measurements a lot of useful information has been collected during the past decade or so which has been further substantiated by collateral evidence from other sources.

Left ventricular stroke work when related to the mean pulmonary wedge pressure has been used in the present investigation as an index of left ventricular performance, while changes in minute work have been taken to represent 'total' energy expenditure of the left ventricle.

9. Mean ejection power index (g.m./sec./sq.m.) The rate of doing work or 'power' of a mechanical pump may alter without change in the total work done. Ventricular performance is therefore assessed both in terms of stroke work and stroke power. It would be highly desirable to have information about instantaneous changes in power, but as yet there is no method to obtain this information in the intact human subject. The mean stroke power has been calculated as:

$$\begin{array}{lcl} \text{Mean ejection stroke} & & \\ \text{power index} & = & \frac{\text{stroke work (g.m./sq.m.)}}{\text{systolic cycle length (sec.)}} \\ \text{(g.m./sec./sq.m.)} & & \end{array}$$

10. Mean ejection flow index (ml./sec./sq.m.) Just as stroke power can change without changes in stroke work, the ejection flow rate can alter without a change in the stroke volume. It is not as yet

technically feasible to measure accurately instantaneous changes in ejection flow rate in the human subject. Only the mean changes were therefore measured.

$$\begin{array}{l} \text{Mean ejection flow index} \\ \text{(ml./sec./sq.m.)} \end{array} = \frac{\text{stroke volume (ml./sq.m.)}}{\text{systolic cycle length (sec.)}}$$

11. Systolic pressure-time index (mm.Hg/sec.). Sarnoff et al (1958) have shown experimentally that the myocardial oxygen consumption correlates best with the pressure-time integral of ventricular contraction - what they have called the "tension-time index". Consideration of the Laplace Law ($P = T/R$) would, however, suggest that the tension in the wall of the ventricle would be greater, for the same systolic pressure, at larger end-diastolic volumes. To save confusion, it would seem more appropriate therefore to term the pressure-time integral simply "systolic pressure-time index".

The systolic pressure-time index may be calculated thus:

$$\text{S.P.T.I. mm.Hg.sec.} = \text{M.S.E.P.} - \text{Mean P.W.P.} \times \text{Duration of systole.}$$

The values have been calculated per stroke as well as per minute.

Recently it has been shown that myocardial contractile element work shows a much better correlation with oxygen consumption (Brittman and Levine, 1964) but this could not be measured in the present studies.

12. Diastolic pressure-time index (mm.Hg.sec.). Coronary filling has been shown to occur for the most part during diastole and would therefore depend upon the duration of diastole and the mean pressure head obtaining during that time. It therefore seems logical to take into account both these variables by calculating the time integral of aortic diastolic pressure.

Thus:

Diastolic Pressure-Time Index, mm.Hg.sec. =

Mean aortic diastolic pressure x Duration of diastole (sec.)
 (mm.Hg.)

This has been calculated per stroke and per minute. The coronary sinus pressure is generally small as compared to the mean aortic diastolic pressure and no correction for this is, therefore, made.

If the coronary vascular resistance does not alter coronary blood flow should be directly related to the diastolic pressure-time index.

C H A P T E R I I I

COMPARISON OF SIMULTANEOUSLY RECORDED PULMONARY WEDGE AND LEFT VENTRICULAR END-DIASTOLIC PRESSURES

Pressure recordings through a catheter 'wedged' in a branch of the pulmonary artery were first obtained in dogs by Hellems et al (1948), and in man by Lagerlöf and Werkö (1949). The significance of such measurements has been a subject of much debate ever since (Wiggers, 1953; Rapaport and Dexter, 1958; and Fishman, 1963). Terms varying from 'pulmonary capillary pressure', 'pulmonary capillary venous pressure', 'pulmonary arterial end-pressure', 'impacted small artery pressure', 'wedged catheter pressure', 'reflected left atrial pressure', and 'pulmonary artery wedge pressure', that have been applied by various authors to this measurement bear testimony to such controversy. Perhaps the term 'pulmonary artery wedge pressure' or more simply 'pulmonary wedge pressure', being descriptive rather than speculative, is the best and as such has found general acceptance. In this study the latter has been used to designate this measurement.

While originally believed to reflect capillary pressure in the pulmonary vascular bed (Hellems et al, 1948 and 1949), later reports demonstrated a close similarity between simultaneously and/or consecutively recorded pulmonary wedge and left atrial pressures in patients with mitral valve disease or atrial septal defects (Epps and Adler, 1953; Werkö et al, 1953; Wilson et al, 1953; Connolly et al, 1953; and 1954; and Rubin and Shah, 1958). Similar agreement has been found during both sinus rhythm as well as atrial fibrillation (Epps and Adler, 1953; Connolly et al, 1954), and even during the Valsalva manoeuvre (Björk et al, 1954). A delay of 0.02 to 0.08 seconds in the pulmonary wedge pressure pulse as compared to the left atrial pulse was observed by Connolly et al (1953) and Epps and Adler (1953). However, other workers have presented data from studies on similar groups of patients, showing a lack of such agreement for both

phasic and mean pressures from the two sites (Murphy, 1958; Bernstein et al, 1960; and Linden and Allison, 1963). Calazel et al (1951) found the mean pulmonary wedge pressure to be in excess of the mean left atrial pressure by 2 mm.Hg when the latter was less than 10 mm.Hg and observed an increase in this gradient at higher levels of pressure. In their studies on eleven patients (normal subjects and patients with mitral valve disease), Luchsinger et al (1962) noted a good correlation ($r = 0.952$) between the two measurements during rest, norepinephrine infusion, and positive or negative intra-alveolar pressures; but in the 42 paired measurements, they found a systematic difference in that the pulmonary wedge pressure was 35% higher than the mean left atrial pressure. In all these studies, however, only a small number of 'spot' observations in individual subjects were examined, and except for the one study mentioned, no attempt at statistical analysis has been made.

Experimental studies in dogs have also produced divergent results. Dow and Gorlin (1950) and Wilson et al (1955) reported close agreement between the pulmonary wedge and left atrial pressures; and Mueller et al (1954) found similar quantitative changes between the two pressures, both before and after occlusion of the aorta. On the other hand, Ankeney (1953) in his studies on dogs did not find any such relationship between the pulmonary wedge and left atrial pressure. However, because of the possible species differences the results from studies in dogs cannot be transposed to the situation in man (Linden and Allison, 1963). At low pressure levels the pulmonary wedge pressure pulse recorded from dogs is a highly damped trace devoid of a waveform (Ankeney, 1953; Mueller et al, 1954). It is possible that the capillary network of dogs is such as to effectively damp out any transmitted pulsations at low pressure levels. On the other hand, adequate pulmonary wedge pressure recordings in man (unlike in dogs) always show a definite

venous pulse waveform, this itself being one of the criteria for a satisfactory pressure record (Rapaport and Dexter, 1958).

In spite of these conflicting reports, the available evidence, on balance, does weigh in favour of a close agreement between the mean pulmonary wedge and left atrial pressures (Fishman, 1963). In fact, many workers, in both clinical and experimental studies, have used the mean pulmonary wedge pressure as an estimate of the mean left atrial pressure.

The mean left atrial pressure has in turn been shown to be almost identical with the left ventricular end-diastolic pressure both in dogs (Mitchell, Gilmore and Sarnoff, 1962), and man (Braunwald, Fishman and Cournand, 1956; Braunwald, Brockenbrough, Frahm and Ross, 1961). It would therefore seem reasonable that the mean pulmonary wedge pressure should also bear a close correlation with the left ventricular end-diastolic pressure. To date no studies attempting to directly relate the two measurements have been reported. The present investigation was undertaken to define the relation between these two measurements in man.

METHODS

Subjects

In 10 male subjects the pulmonary wedge pressure and left ventricular end-diastolic pressure were simultaneously recorded. Of these, four were normal subjects without any detectable cardiovascular abnormality or systemic disorder of any haemodynamic significance; four patients had systemic arterial hypertension with radiological and electrocardiographic evidence of left ventricular enlargement; and two patients were in atrial fibrillation, both without detectable valvular heart disease. Their ages ranged between 15 and 59 years. The relevant clinical details of the subjects are presented

in Table 3.

Plan of Investigation

To compare pressures over a wide range, measurements were made both at rest in the supine position and during multiple levels of supine leg exercise performed on a bicycle ergometer coupled to the table on which the patient was lying. The levels of exercise were chosen to suit the performance of each subject, and were not therefore comparable between subjects. Resting observations were first made for a variable period of 20 to 30 minutes, following which the subjects exercised for another 15 to 30 minutes.

Details of the techniques used, as also the frequency response characteristics of the catheter-manometer systems, have been given in Chapter II.

Continuous recordings of both pressures were made for a period of 15 seconds in each minute at a paper speed of 135.4 mm./sec. to obtain adequate spread of pressure events. Electrically integrated mean pulmonary wedge pressure was synchronously and continuously recorded with the phasic pressure trace. The pressures were calibrated against an open saline-filled column common to both.

Left ventricular end-diastolic pressure was identified as the short step at which the ventricular diastolic pressure levels off immediately prior to the steep rise of pressure during isovolumic contraction. Corresponding points on the pulmonary wedge pressure pulse also showing a similar level pressure at the 'z' point (immediately following the 'a' wave, Werle et al, 1942) were then measured. Only well identifiable points on the simultaneously recorded pressure pulses were accepted. A variable time delay was noted between the two pressures by this technique, the former

leading the latter by 0.05 to 0.08 seconds.

Details of the statistical methods used are given in the appendix.

RESULTS

Between 320 and 328 comparisons of simultaneously recorded 'z' point pulmonary wedge and left ventricular end-diastolic pressures were made in each subject (Tables 4 to 13). The overall range of the pressures thus compared was 1 to 49 mm.Hg. A close agreement between the two pressures was noted in each instance. Representative samples of measurements made at rest and during exercise showing the striking similarity in both the direction and magnitude of the beat to beat changes, in each patient, are shown in Figs. 12 to 14. Respiratory variations were noted in both pressures. To illustrate this, a few periods showing marked changes in the two pressures during voluntary hyperventilation have been deliberately chosen in some of the subjects (A.W., M.G., L.B. and W.A.).

For detailed comparison, the pairs of individual pressure measurements in each patient and their respective minute averages in each group of patients were statistically analysed and the results are summarised in Tables 14 and 15 respectively.

A striking linear relationship between the two pressures with only a narrow distribution of the comparative observations about the regression line was seen in all patients. No systematic error was observed in any of them. In all but one instance, the slope of the regression line was so close to a unit slope, the line itself passing near the origin (Table 14), that for purposes of diagrammatic representation only the line of identity has been drawn for 9 of the 10 patients in Figs. 15, 16 and 17. Patient W.A., who was in atrial fibrillation, was the only subject in whom the regression line

COMPARISON OF SIMULTANEOUSLY RECORDED LEFT VENTRICULAR END-DIASTOLIC
AND PULMONARY WEDGE PRESSURES AT REST AND DURING EXERCISE IN NORMAL SUBJECTS

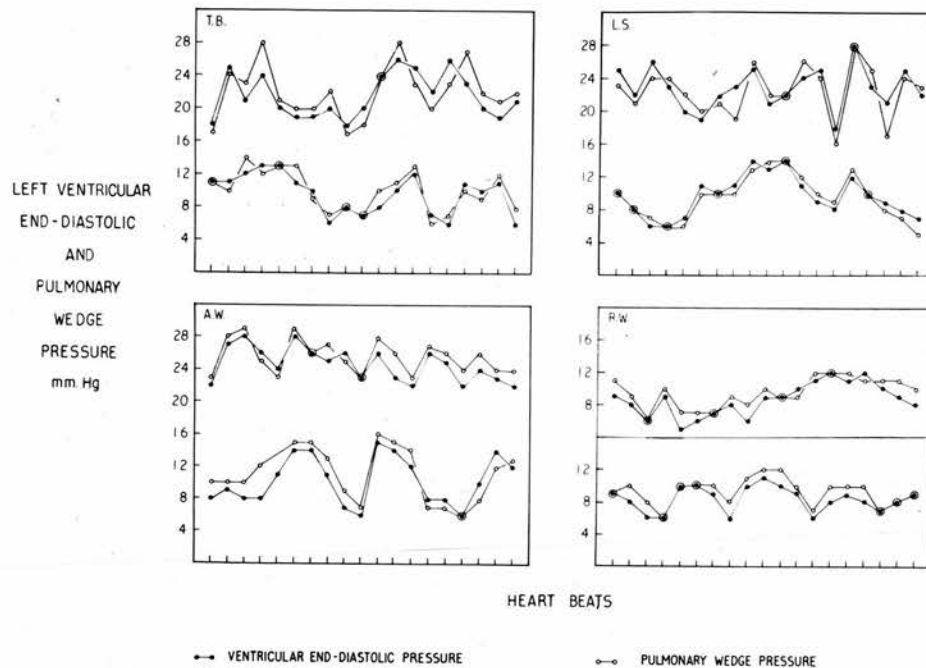


Figure 12

Comparison of simultaneously recorded left ventricular end-diastolic and pulmonary wedge pressures at rest and during exercise in normal subjects. The upper row figures obtained during exercise. The lower row figures obtained during rest. The beat to beat fluctuations during resting measurements seen in patients A.W. and R.W. were observed during periods of voluntary hyperventilation.

COMPARISON OF SIMULTANEOUSLY RECORDED LEFT VENTRICULAR END-DIASTOLIC
AND PULMONARY WEDGE PRESSURES AT REST AND DURING EXERCISE IN HYPERTENSIVE PATIENTS

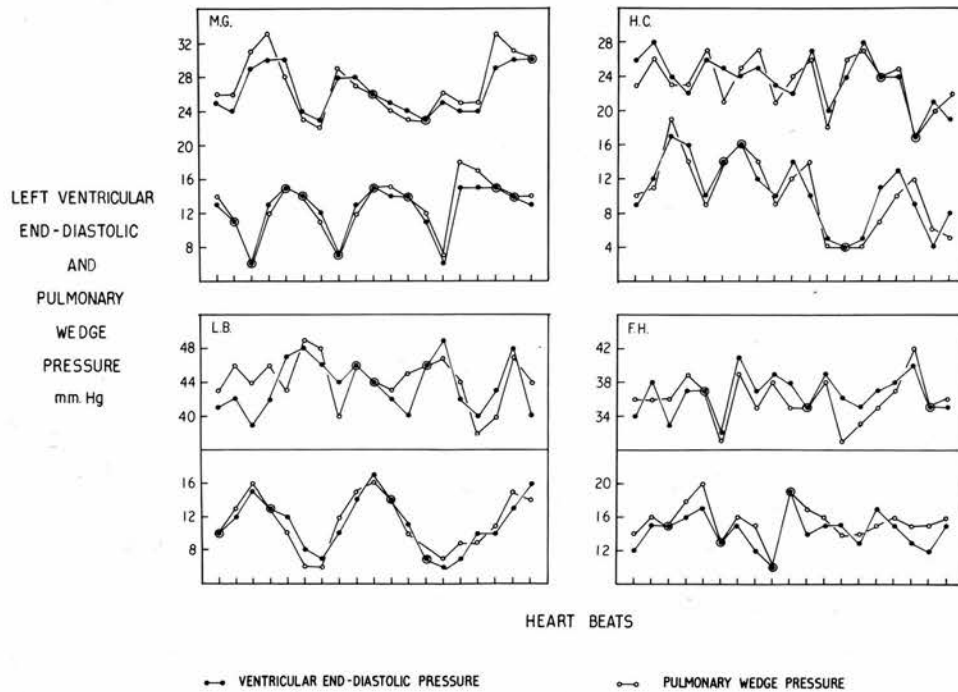


Figure 13

Comparison of simultaneously recorded left ventricular end-diastolic and pulmonary wedge pressures at rest and during exercise in hypertensive patients. The upper row figures obtained during exercise. The lower row figures obtained during rest. The beat to beat fluctuations during resting measurements seen in patients M.G. and L.B. were observed during periods of voluntary hyperventilation.

COMPARISON OF SIMULTANEOUSLY RECORDED LEFT VENTRICULAR END-DIASTOLIC
AND PULMONARY WEDGE PRESSURES AT REST AND DURING EXERCISE IN PATIENTS WITH ATRIAL FIBRILLATION

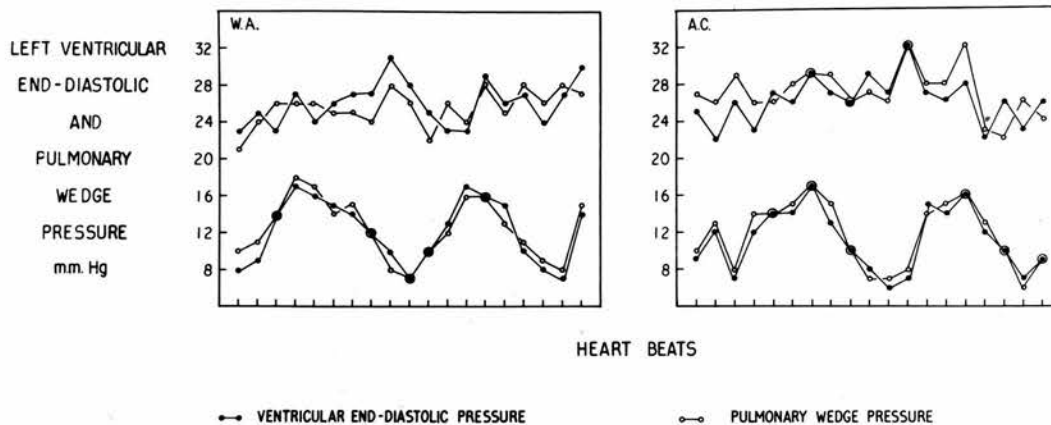


Figure 14

Comparison of simultaneously recorded left ventricular end-diastolic and pulmonary wedge pressures at rest and during exercise in patients with atrial fibrillation. The upper row figures obtained during exercise. The lower row figures obtained during rest.

COMPARISON OF SIMULTANEOUSLY RECORDED LEFT VENTRICULAR END-DIASTOLIC AND PULMONARY WEDGE PRESSURE
AT REST AND DURING EXERCISE IN NORMAL SUBJECTS

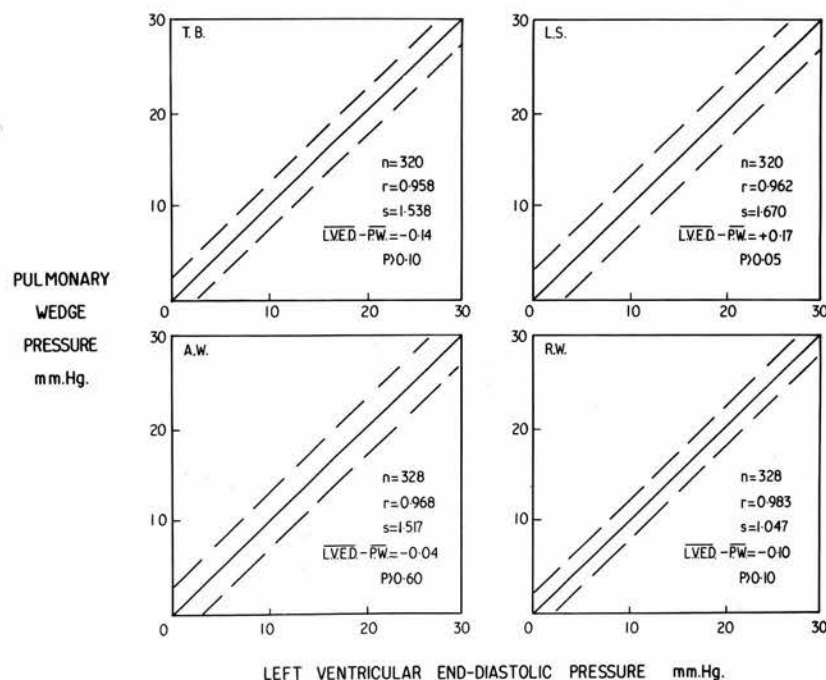


Figure 15

Comparison of simultaneously recorded left ventricular end-diastolic and pulmonary wedge pressures at rest and during exercise in normal subjects. Individual observations have not been plotted because of their large number. "n" = number of observations, "r" = correlation coefficient, "s" = standard error of estimate. The confidence intervals calculated from the standard error of estimate are represented by the interrupted lines.

COMPARISON OF SIMULTANEOUSLY RECORDED LEFT VENTRICULAR END-DIASTOLIC AND PULMONARY WEDGE PRESSURE
AT REST AND DURING EXERCISE IN HYPERTENSIVE PATIENTS

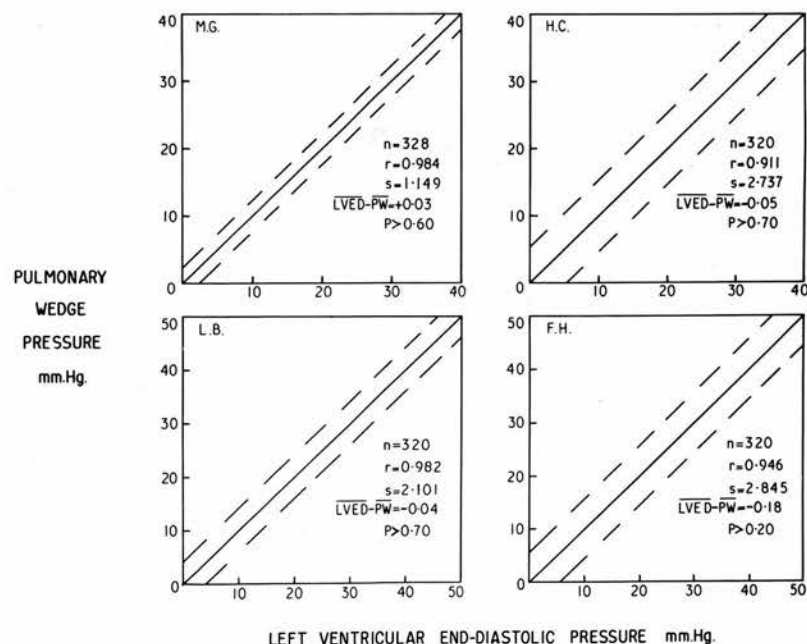


Figure 16

Comparison of simultaneously recorded left ventricular end-diastolic and pulmonary wedge pressures at rest and during exercise in hypertensive patients. Individual observations have not been plotted because of their large number. "n" = number of observations, "r" = correlation coefficient, "s" = standard error of estimate. The confidence intervals calculated from the standard error of estimate are represented by the interrupted lines.

COMPARISON OF SIMULTANEOUSLY RECORDED LEFT VENTRICULAR END-DIASTOLIC AND PULMONARY WEDGE PRESSURE
AT REST AND DURING EXERCISE IN PATIENTS WITH ATRIAL FIBRILLATION

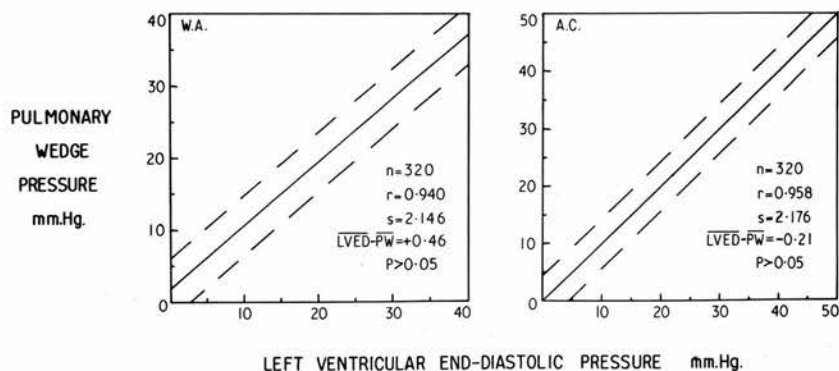


Figure 17

Comparison of simultaneously recorded left ventricular end-diastolic and pulmonary wedge pressures at rest and during exercise in patients with atrial fibrillation. The slope of the regression line in patient W.A. was found to be significantly different from the unit slope. Individual observations have not been plotted because of their large number. "n" = number of observations, "r" = correlation coefficient, "s" = standard error of estimate. The confidence intervals calculated from the standard error of estimate are represented by the interrupted lines.

was significantly different from the line of identity (Fig. 17). The 95% confidence limits, calculated from the standard error of estimate, are shown by the interrupted lines in these diagrams. Because of their very large number, individual observations have not been plotted.

In the four normal subjects the correlation coefficients ranged between 0.958 and 0.983 (Table 14). The small standard error of estimate, ranging between 1.047 and 1.670 in individual subjects, implies that if the 'z' point pulmonary wedge pressure be used as an estimate of left ventricular end-diastolic pressure the error would be less than ± 3 mm.Hg in 95% of observations.

A similar close correlation between the two pressures was demonstrated in each of the four hypertensive patients (r between 0.911 and 0.984). The standard error of estimate in these patients varied between 1.149 and 2.845 (Table 14). Thus, while in two patients (H.C. and F.H.) the 'z' point pulmonary wedge pressure if used as an indirect estimate of left ventricular end-diastolic pressure would have been in error by less than ± 6 mm.Hg in 95% of instances, in the two other the likely error was much smaller, being within ± 4 mm.Hg in one subject (L.B.) and only ± 2 mm.Hg in the other (M.G.).

In the two patients with atrial fibrillation but without any detectable valvular heart disease the correlation coefficients were again of a similar high order ($r = 0.940$ and 0.958). As already stated, the regression equation in one of these patients (.W.A.) revealed a slight bias so that at low pressure levels, the 'z' point pulmonary wedge pressure tended to be slightly higher than the left ventricular end-diastolic pressure, while at higher pressure levels this relationship was reversed. The second patient (A.C.), however, did not show any such discrepancy, the regression line being close to the line of identity (Table 14, Fig. 17). The standard error of estimate

in these two patients was 2.146 and 2.176 respectively; so that in 95% of instances, in either case, the 'z' point pulmonary wedge pressure was within ± 4 mm.Hg of any given left ventricular end-diastolic pressure.

Evidence of the close agreement between the two pressure measurements is also given by the frequency distributions of the differences between individual pairs of measurements in each patient (Table 16), illustrated in Fig. 18. While the range of such differences in the group of normal subjects was -5 to +6 mm.Hg, 95% of observations fell within ± 2 mm.Hg. Again, in the four hypertensive patients, while the maximum observed differences were -7 and +7 mm.Hg, in 71% of instances these were actually within ± 2 mm.Hg and in 94% within ± 4 mm.Hg. Similarly, in the two patients with atrial fibrillation, although these differences ranged between -6 and +6 mm.Hg, 72% of the observations were with ± 2 mm.Hg and 96% within ± 4 mm.Hg.

The overall means of the 'z' point pulmonary wedge and left ventricular end-diastolic pressures in individual subjects were also compared. Using the 'Student's' t test, the differences between the two means were found to be not significant in all except one patient (W.A.) who was in atrial fibrillation (Table 14).

Since, in practice, time averaged pressure measurements are generally examined, individual values of simultaneously recorded left ventricular end-diastolic and 'z' point pulmonary wedge pressures obtained in each minute were averaged, and these averages subjected to similar statistical analysis. To identify possible differences in the comparison of the two pressure measurements made during rest and exercise, these were separately analysed. In each subject 18 such minute averaged figures of either pressure obtained during rest and a further 12 during exercise were thus available for comparison. The data from individual subjects in each group were pooled together so that

FREQUENCY DISTRIBUTIONS OF THE DIFFERENCES BETWEEN PAIRS OF SIMULTANEOUSLY RECORDED
LEFT VENTRICULAR END-DIASTOLIC AND PULMONARY WEDGE PRESSURES IN INDIVIDUAL SUBJECTS

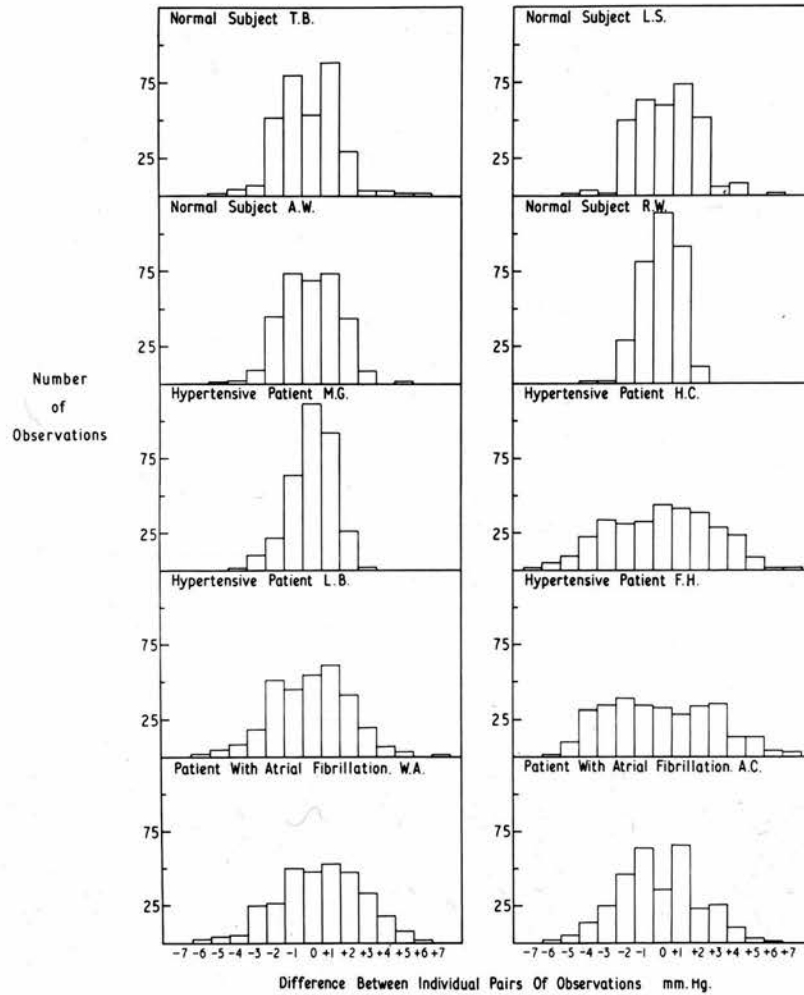


Figure 18

Frequency distributions of the differences between pairs of simultaneously recorded left ventricular end-diastolic and pulmonary wedge pressures in individual subjects.

in the groups of normal subjects and hypertensive patients 72 comparisons of resting figures and 48 of exercise figures were made, while in the group of patients with atrial fibrillation 36 and 24 respective comparisons were made. The results of these analyses, summarised in Table 15, again demonstrated the close correlation between the two pressures in all three groups of subjects, both for resting and exercise measurements.

A linear relationship between the averaged left ventricular end-diastolic and 'z' point pulmonary wedge pressures was seen in all six of these comparisons (Figs. 19, 20 and 21). The regression line, in all instances, was so close to the line of identity that only the latter has been drawn in these diagrams. The narrow scatter of the comparative observations about the regression line is evidenced by the very high degree of correlation between the two measurements ($r = 0.932$ to 0.989 and $S = 0.627$ to 1.272). No difference between the comparisons of the resting and exercise measurements was seen in any of the three groups. Although the standard error of estimate tended to be a slightly higher figure for the exercise measurements as compared to the resting ones, the difference in fact was marginal and probably of little significance. In the group of normal subjects the deviation of the 'z' point pulmonary wedge pressure from the 'true' left ventricular end-diastolic pressure in any 95 of 100 observations was not greater than ± 1 mm.Hg during rest and ± 2 mm.Hg during exercise ($S = 0.628$ and 0.964 respectively). Corresponding figures for the other two groups were ± 2 mm.Hg for both resting ($S = 0.829$ and 0.781) and exercise ($S = 1.272$ and 1.204) measurements.

The frequency distributions of the differences between the minute averaged values are given in Table 17. The overall distribution of these differences in all subjects is shown in Fig. 22. The differences are seen to be distributed within a very narrow range, 94% of the total observations

COMPARISON OF AVERAGE MINUTE VALUES OF SIMULTANEOUSLY RECORDED LEFT VENTRICULAR END-DIASTOLIC
AND PULMONARY WEDGE PRESSURE AT REST AND DURING EXERCISE IN NORMAL SUBJECTS

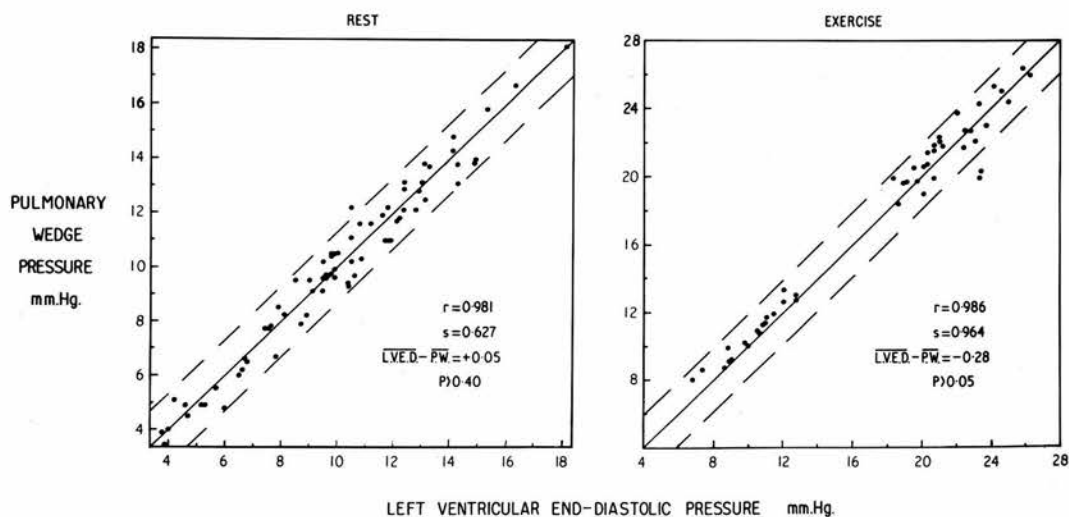


Figure 19

Comparison of average minute values of simultaneously recorded left ventricular end-diastolic and pulmonary wedge pressures at rest and during exercise in normal subjects. "r" = correlation coefficient, "s" = standard error of estimate. The confidence intervals calculated from the standard error of estimate are shown by the interrupted lines.

COMPARISON OF AVERAGE MINUTE VALUES OF SIMULTANEOUSLY RECORDED LEFT VENTRICULAR END-DIASTOLIC
AND PULMONARY WEDGE PRESSURE AT REST AND DURING EXERCISE IN HYPERTENSIVE PATIENTS

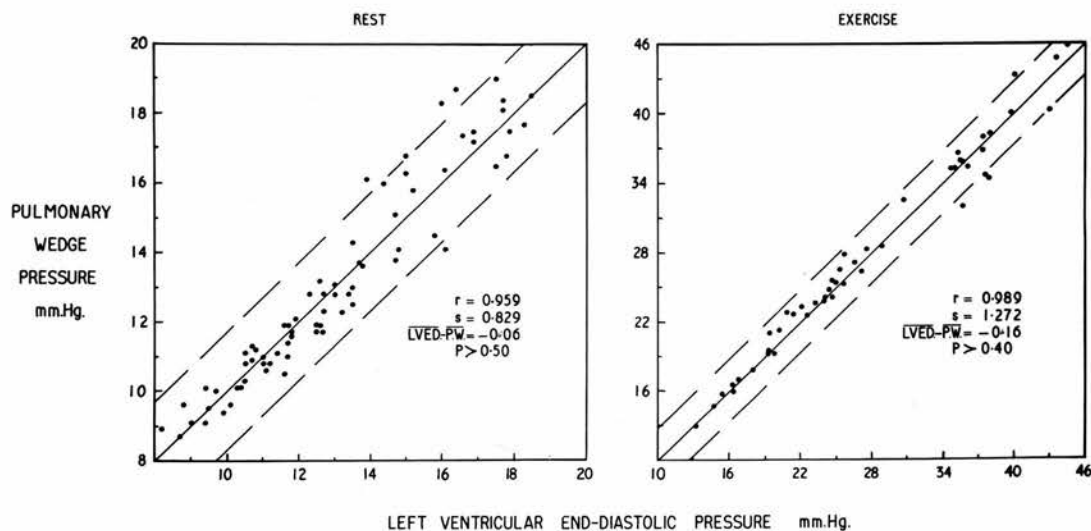


Figure 20

Comparison of average minute values of simultaneously recorded left ventricular end-diastolic and pulmonary wedge pressures at rest and during exercise in hypertensive patients. "r" = correlation coefficient, "s" = standard error of estimate. The confidence intervals calculated from the standard error of estimate are shown by the interrupted lines.

COMPARISON OF AVERAGE MINUTE VALUES OF SIMULTANEOUSLY RECORDED LEFT VENTRICULAR END-DIASTOLIC AND PULMONARY WEDGE PRESSURE AT REST AND DURING EXERCISE IN PATIENTS WITH ATRIAL FIBRILLATION

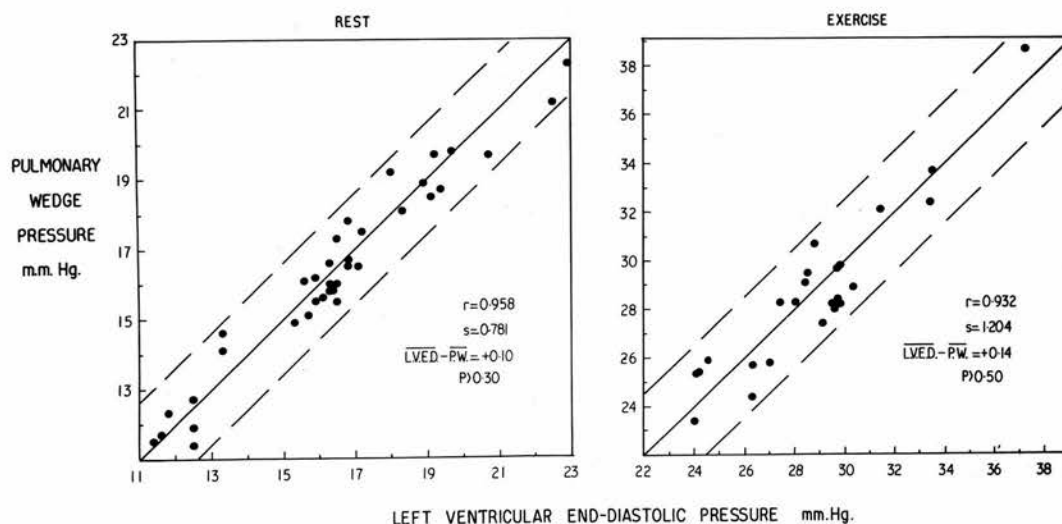


Figure 21

Comparison of average minute values of simultaneously recorded left ventricular end-diastolic and pulmonary wedge pressures at rest and during exercise in patients with atrial fibrillation. "r" = correlation coefficient, "s" = standard error of estimate. The confidence intervals calculated from the standard error of estimate are shown by the interrupted lines.

FREQUENCY DISTRIBUTION OF THE DIFFERENCES BETWEEN MINUTE AVERAGED PULMONARY WEDGE
AND LEFT VENTRICULAR END-DIASTOLIC PRESSURES IN ALL GROUPS OF PATIENTS

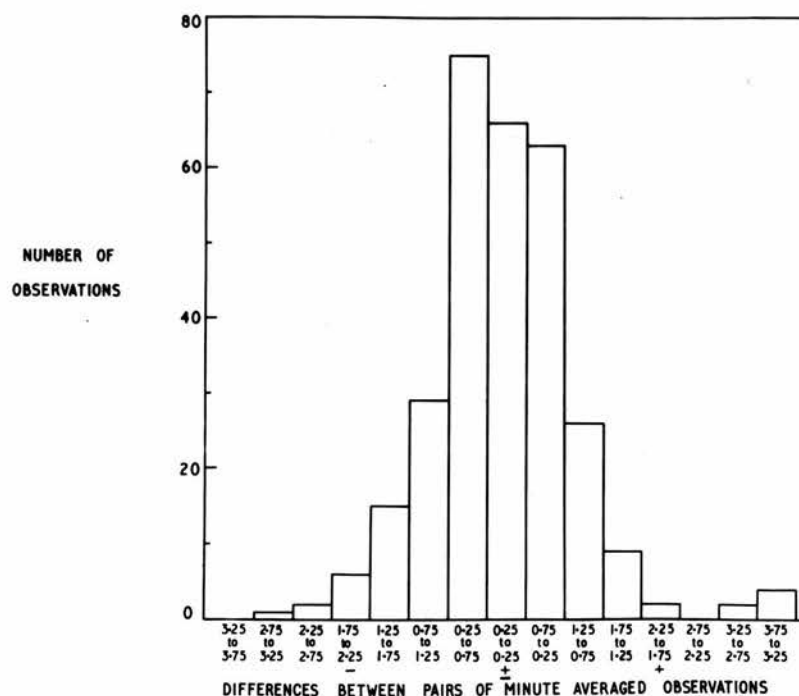


Figure 22

Frequency distribution of the differences between minute averaged pulmonary wedge and left ventricular end-diastolic pressures in all groups of patients.

falling within three class intervals (each of 0.5 mm.Hg) on either side of the mean, i.e. within ± 2 mm.Hg.

In order to examine the relationship between the 'z' point and mean pulmonary wedge pressures, the records of two normal subjects (R.W. and A.W.) showing periods of relatively stable pressures extending over two or more complete respiratory cycles were further examined. The electrically integrated mean pressure was measured and all the 'z' point pressures during each such period averaged. A total of 84 such periods were thus compared. Of these, 48 periods (R.W. = 20 and A.W. = 28) were taken from resting measurements and 36 periods (R.W. = 16, and A.W. = 20) from exercise measurements. No significant difference was found between the variances of the resting and exercise measurements and therefore the data was pooled together. A very good correlation ($r = 0.971$) between the mean pulmonary wedge and corresponding 'z' point pressures was found (Fig. 23). The regression line was not significantly different from a unit slope nor was a significant intercept demonstrated. The standard error of estimate was 1.121 showing that the averaged 'z' point pressures were within ± 2 mm.Hg of the mean pulmonary wedge pressure for that period. The difference between the overall means of these observations (0.4 mm.Hg) was not statistically significant ($p > 0.6$).

DISCUSSION

While there is no a priori reason why the mean pulmonary wedge pressure should reflect accurately the left ventricular end-diastolic pressure or the mean left atrial pressure, the presumption is that the process of 'wedging' a catheter in a branch of the pulmonary artery results in a static column of

COMPARISON OF AVERAGED 'Z' POINT PULMONARY WEDGE
AND INTEGRATED MEAN PULMONARY WEDGE PRESSURES
IN TWO SUBJECTS DURING REST AND EXERCISE

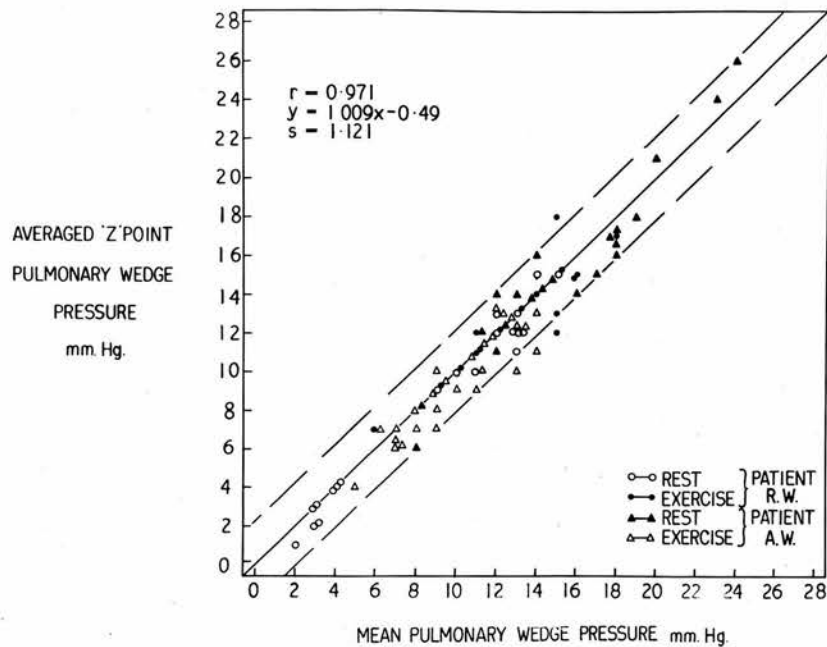


Figure 23

Comparison of averaged "z" point pulmonary wedge and integrated mean pulmonary wedge pressures in two subjects during rest and exercise. "r" = correlation coefficient, "s" = standard error of estimate. The confidence intervals calculated from the standard error of estimate are shown by the interrupted lines.

blood extending from the tip of the catheter to the pulmonary veins, the left atrium (Fishman, 1963) and the diastolic left ventricle. In the absence of valves in the pulmonary circulation, and any significant anastomoses between the pulmonary arteries themselves or between these and the bronchial arteries, it is thought possible that such a static column of blood may in fact be established provided that the pulmonary vasculature is normal (Fishman, 1963). Although no direct proof of this hypothesis is available, it has been shown, in dogs, that occlusion of a pulmonary artery results in a drop in pressure distal to the site of occlusion to the same level as recorded through the 'wedged' catheter (Mueller et al, 1954). It has also been shown by similar occlusion experiments in man that the pressure in the pulmonary artery itself does not influence the pulmonary wedge pressure (Werkö et al, 1953).

In this study only the pressure at the 'z' point of the pulmonary wedge pulse wave was initially examined since it is at this time in the cardiac cycle that pressure in the column of blood extending from the tip of the 'wedged' catheter to the cavity of the left ventricle can be expected to equilibrate. Further, if this is the pressure in a single static column of fluid, it must also represent the mean pressure in the 'system' around which phasic changes will oscillate, particularly since, in the absence of obstruction at the mitral valve, there are no large pressure generating regions in it. The 'system' from this viewpoint consists of the length of the pulmonary vasculature in front of the catheter tip, the left atrium and the 'relaxed' left ventricle. The absolute level of this pressure will vary with changes in the volume and compliance of the whole 'system'. It, therefore, seems reasonable to expect that the mean pulmonary wedge pressure will correspond with the 'z' point pressure. In the present study, the

electrically integrated mean pressure was seen to follow closely the 'z' point pressure in all subjects, and during periods of stable pressures the two were almost identical. Because of a time delay introduced by the circuit, the electrically integrated mean pressure could not be used for comparative analysis in all subjects since rapidly changing pressures in successive cardiac cycles were measured. However, in two normal subjects sufficiently long strips of reasonably stable pressures were available, and in these a close correlation between the mean pulmonary wedge and corresponding 'z' point pressures has been demonstrated. Collateral evidence in support of this hypothesis is also provided by the studies of Braunwald et al (1961) who have shown that the left atrial mean pressure (mean 7.1, range 1 - 12 mm.Hg) is almost the same as the 'z' point pressure on the left atrial pulse (mean 7.6, range 1 - 13 mm.Hg). The author would like to emphasise, however, that it is no part of this argument that phasic changes in the pulmonary wedge pressure will reflect accurately similar changes in the left atrial pressure pulse. On the contrary, it would be expected that the pulmonary wedge pressure pulse would at best be only an unpredictably damped version of the left atrial pulse. Failure to distinguish between these two arguments seems to have led to much confusion in the past.

The importance of mean pulmonary wedge pressure measurement, in practice, is two-fold. As an indirect estimate of left ventricular filling pressure, it can be used to assess left ventricular performance in man without the need for left ventricular catheterisation to obtain this measurement alone. The limitations in the use of either pressure measurement in this sense would be the same, i.e. the pressure-length relationship of the myocardium is not linear but parabolic. Secondly, as a measure of mean left atrial pressure it is of value in assessing the degree of obstruction

at the mitral valve, and also in a more limited sense changes in the pulmonary circulation. The present study was designed to elucidate the first of these and the striking agreement between the two pressures demonstrated would justify the use of mean pulmonary wedge pressure as an indirect estimate of left ventricular filling pressure. This relationship has been shown to hold in normal subjects, in patients with left ventricular enlargement and those in atrial fibrillation (in the absence of obstruction to blood flow at the mitral valve), for all pressures ranging between 1 and 49 mm.Hg. Furthermore, measurements made at rest and during exercise, over a wide range of flow rates, show a similar degree of agreement. Although the likely error in single estimations in some instances may seem to be rather large, this, as would be expected, was greatly reduced when time averaged pressures were compared. Percentage error would, however, be greatest at low pressure levels as compared to the higher ranges of pressure. While it is possible that the observed differences between the two pressures were in part due to the likely variations in the position of the pulmonary wedge catheter with respect to the cavity of the left ventricle, this seems unlikely to have been a major factor since it would have resulted in a systematic error which was not observed in any subject.

There are two pathological states in which the author feels that the mean pulmonary wedge pressure may not bear a definite relation to the left ventricular end-diastolic pressure. The first of these is obstructive airways disease where fortuitous positioning of the catheter tip in the vicinity of a segment with air trapping may result in falsely high pressures. The second is regurgitation at the mitral valve when large systolic pressure waves may again result in high readings of mean pulmonary wedge pressure.

In the latter situation, the 'z' point pressure should still reflect accurately the left ventricular end-diastolic pressure. Further, in situations where atrial systole produces a large pressure pulse (e.g. restrictive myocardial or pericardial disease) a systematic difference between the mean pulmonary wedge and left ventricular end-diastolic pressure may be expected.

Mitchell, Gilmore and Sarnoff (1962) have recently defined the factors affecting the relationship between the mean left atrial pressure and left ventricular end-diastolic pressure in dogs. Stimulation of the stellate ganglion so modifies this relationship that for any given left ventricular end-diastolic pressure the mean left atrial pressure is lower than in the control studies. The reverse has been noted during efferent vagal stimulation. These changes have been interpreted as suggesting altered pressure-volume relationship of the atrium rather than the ventricle, since in another study from the same laboratory (Mitchell, Linden and Sarnoff, 1960) it has been shown that these stimuli do not alter the pressure-length relationship of the ventricular muscle. It seems possible, therefore, that the measured mean left atrial or pulmonary wedge pressure may in some circumstances be higher or lower than the 'true' left ventricular end-diastolic pressure, but as yet there is no evidence for this in human studies. Exercise, in the present study, has been shown not to alter this relationship.

SUMMARY AND CONCLUSIONS

The study reported in this chapter was designed to determine the confidence with which the mean pulmonary wedge pressure could be used as an estimate of left ventricular end-diastolic pressure in man. The results

obtained, from the beat by beat comparison of the simultaneously recorded 'z' point pulmonary wedge and left ventricular end-diastolic pressures, have shown a close agreement between the two over a wide range of pressure measurements (1 to 49 mm.Hg). A similar order of correlation was found in each of the normal subjects as well as patients with left ventricular enlargement (hypertensive patients), and those with atrial fibrillation but without mitral valve disease. Further, no significant differences were found when the measurements obtained at rest and those obtained during supine leg exercise were separately compared in each of the three groups of subjects. Evidence of a close correlation between the mean pulmonary wedge pressure and the averages of the corresponding 'z' point pressures has also been presented.

On the strength of this information, it is concluded that, in certain circumstances, the mean pulmonary wedge pressure is a reasonably accurate measure of the 'true' left ventricular end-diastolic pressure and can, therefore, be used to assess left ventricular performance in man. Theoretical arguments in support of the findings have been presented. Some limiting circumstances, in which the results of the present study may not be valid, have also been indicated.

C H A P T E R I V

HAEMODYNAMIC CHANGES FOLLOWING INTRAVENOUS INJECTION OF MORPHINE WITH PARTICULAR REFERENCE TO CHANGES IN LEFT VENTRICULAR PERFORMANCE

Few drugs considered to be of therapeutic value in modern medical practice can claim to have withstood the rigorous test of time as morphine has. In spite of several disadvantages in its use, in particular tolerance and physical dependence, and concerted research to find a superior substitute, morphine remains the analgesic par excellence.

Morphine is the principal alkaloid found in opium (10% by weight) which is the dried and powdered residue from the milky exudate obtained from unripe capsules of *papaver somniferum*. The use of opium as a medicament probably dates back to antiquity. Both words "opium" and "morphine" are derived from Greek (Goodman and Gillman, 1965). The earliest known reference to the medicinal use of poppy juice is said to be found in the works of Theophrastus (3rd Century, B.C.). Morphine itself was isolated in 1803 by a young German pharmacist, Sert^uturner (Reynolds and Randall, 1957). The chemical structure of morphine has been established by Gates and Tschudi (1952). The phenolic and alcoholic hydroxyl groups at positions 3 and 6 on the phenanthrene nucleus and the nitrogen bridge with the attached methyl group are considered to be essential for the pharmacological actions of the drug (Reynolds and Randall, 1957; and Goodman and Gillman, 1965).

The pharmacological actions of morphine are diverse and involve almost all organ systems to a greater or lesser degree. While some of these actions have been studied extensively, others have not engaged the attention of many workers. Several reviews of the pharmacological actions of morphine are available, the most extensive of these are by Krueger, Eddy and Sumwalt (1941) and Reynolds and Randall (1957). Amongst other reviews, though more limited in scope, are those of Wikler (1950) and Eckenhoff and Oech (1960).

In spite of widespread use in clinical practice, and the frequent

claim that morphine is a "specific" drug for the treatment of left ventricular failure and is invaluable in other cardiovascular disorders, the circulatory effects of morphine in man have not been adequately explored. The little information that is available on this subject has come mainly from workers in the field of anaesthesiology. It appears that the generally negative results reported during the 1930s and 1940s have inhibited further work in this field. Much of the earlier work was performed on animals. The marked species differences in the pharmacological actions of morphine (Reynolds and Randall, 1957) severely limits the application of information obtained from animal studies to the situation in man. The premedication and anaesthesia used in the course of the animal studies could also have influenced the results. Furthermore, the dosage of morphine used in animal studies is, weight for weight, far in excess of that ever used in man. Only a few studies on man have been reported. A brief review of some of these reports follows but no attempt has been made to present an exhaustive survey of the literature which is available in the aforementioned reviews.

Resnik et al (1935) were probably the first to study the circulatory effects of morphine in two patients with syphilitic aortic incompetence who were in cardiac failure. Two hours after the administration of morphine (20 and 15 mg.) the cardiac output (acetylene method) and heart rate decreased in both patients. Relief from dyspnoea was noted at this time.

Starr et al (1937) administered morphine subcutaneously to eight normal subjects (Average dose 14 mg.) and an equal number of patients with heart disease but not in cardiac failure (average dose 19 mg.). The cardiac output was measured by the ethyl iodide technique and blood pressure by means of a sphygmomanometer. Measurements were made in the supine position before and between $\frac{1}{2}$ to $1\frac{1}{2}$ hours after the drug. No statistically

significant changes were found in either heart rate, blood pressure, or cardiac output.

Wangeman and Hawk (1942) studied changes in respiration, blood pressure, heart rate and oxygen consumption in five subjects given 16.2 mg. of morphine sulphate subcutaneously. Variable changes in blood pressure and pulse rate were observed during the six hour study period. Oxygen consumption generally decreased and so did respiratory frequency and minute volume.

Papper and Bradley (1942) administered morphine (10 mg) intravenously to six normal subjects (posture not stated, but almost certainly supine). No consistent changes were found in pulse rate or blood pressure but the cardiac output (ballistocardiograph) increased in two subjects immediately after ($1\frac{1}{2}$ minutes) the injection of morphine, while a delayed (10 to 60 minutes) rise was observed in another subject. The calculated systemic vascular resistance varied inversely with the changes in cardiac output. The subjects complained of a "transient head pain which appeared immediately after administration".

Similar results were also reported by Drew et al (1946) in normal supine subjects given 10 to 20 mg. of morphine sulphate intravenously. The heart rate increased immediately in 18 of the 19 subjects but had returned to control levels by 10 minutes in 16 subjects. Systolic blood pressure was measured (sphygmomanometer) in 11 subjects and this increased in six, decreased in two and did not change in three subjects. Cardiac output (ballistocardiograph) was measured in seven subjects and six of these showed an immediate increase (at 1 to 2 minutes) which was largely due to the increase in heart rate. When the measurements were repeated at 40 minutes essentially normal figures were obtained. The authors

concluded that the only significant changes were "the immediate increase in pulse rate and cardiac output." Intramuscular injections resulted in even less of a change. They then proceeded to study the effects of tilting the patients into a 75° head up position before and 30 minutes after injection of morphine. 25 subjects were studied in this way and 11 of these "either fainted or showed signs and symptoms indicative of imminent circulatory collapse" within 4 to 14 minutes of the injection. No distinction could be made between the "fainters" and "non-fainters" on the basis of their reactions to tilting before the injection of morphine, or changes in respiratory function. When the legs and thighs were bandaged in the 11 "fainters" before tilting them for the third time, the symptoms and signs were reproduced in only two subjects. Fainting was associated with a fall in blood pressure (attributed to peripheral vasodilatation) and either bradycardia or tachycardia.

Johnson (1951) administered morphine and scopolamine (6 to 18 mg. of morphine) to nine normal subjects and found a mean fall of 9% in cardiac output and 6% in oxygen consumption, 20 to 50 minutes after administration of the drug. Although average systolic and diastolic blood pressure fell by 9 and 7 mm.Hg respectively, the peripheral vascular resistance increased by 5%. Mean pulmonary artery pressure did not change significantly except in one subject in whom it increased by 6 mm.Hg. The pulmonary vascular resistance increased by an average of 21% in the group. In view of the combination of drugs used in this study it is difficult to evaluate the results.

Fejfar et al (1957) obtained haemodynamic measurements in 21 patients with mitral stenosis given 10 mg. of morphine intravenously. The cardiac output (direct Fick method), measured 10 to 15 minutes after the injection,

increased in nine, decreased in six and did not change in five patients. The increase in cardiac output was found in patients who had a low figure initially. Systemic vascular resistance changed inversely with the changes in cardiac output. Mean pulmonary artery pressure increased in 20 patients while a decrease was noted in one patient who developed pulmonary oedema during the procedure. Heart rate increased initially in 16 patients but this was not considered to be significant by the authors. Minute ventilation decreased in all subjects. One patient who developed pulmonary oedema and was given morphine showed an increase in cardiac output, and a decrease in heart rate, mean pulmonary artery pressure and systemic and pulmonary vascular resistances.

Thomas et al (1965) administered morphine sulphate (3 to 16 mgs.) as a slow infusion (1 mg./min.) to 13 patients with acute myocardial infarction. The study was repeated on two of them within 24 hours. A transient fall in blood pressure was observed in eight instances. In one of these the blood pressure decreased rapidly to almost "shock" levels so that infusion of the drug had to be discontinued. The systemic vascular resistance decreased in eight instances and did not change in seven. Variable changes were observed in heart rate and stroke volume. The cardiac output (dye method using an ear-piece oximeter) did not change in seven instances, while it increased, for part or whole of the study period, in another eight instances. Changes in pulmonary circulation were not studied. No statistical treatment of the data was undertaken.

Roy et al (1965) studied the effect of morphine (10 mg.), injected as a bolus into the pulmonary artery, in four patients who had recovered

from high altitude pulmonary oedema. The acute episode in these patients had occurred 20 to 67 days prior to the study. From the data provided all patients had a normal resting haemodynamic pattern at the time of the study. The most significant change observed and commented upon by the authors, was a decrease in pulmonary blood volume which was estimated by consecutive injections of dye (indigo-carmin) into the pulmonary artery and left atrium while sampling from the femoral artery. Measurements of cardiac output were made 15 minutes after the injection of morphine. Although they make no comments on the rest of their findings, it is evident from the data provided that the mean femoral artery, pulmonary artery, left atrial and right atrial pressures also decreased in all subjects. Likewise, the cardiac output, heart rate, stroke volume, and the left and right ventricular minute work decreased. Variable changes occurred in the systemic vascular resistance.

It is apparent from these studies that, despite statements to the contrary, morphine produces definite haemodynamic changes. The therapeutic efficacy of the drug in acute left ventricular failure is well-established on the basis of clinical usage, and indeed it is considered to be one of the first lines of treatment in this disorder. However, there is no documented evidence about the precise manner in which morphine influences the circulation, particularly in acute left ventricular failure, and the varied hypotheses that have been advanced make an interesting study of the preferences of individual authors. It was therefore felt that a fresh study of the circulatory changes following administration of morphine was desirable so as to delineate as far as possible its precise mode of action in acute left ventricular failure. The present study was undertaken with this in view. In order to be able to make a thorough

assessment, with the aid of modern techniques, of as many haemodynamic parameters as possible it was thought best to confine the study to one hour after the injection of morphine. The intravenous route of administration was chosen to ensure uniformity of absorption and distribution. Normal subjects, patients in acute left ventricular failure and those with mitral valve disease were chosen to cover a wide range of cardiovascular abnormality. Of necessity, because of the availability of patient material and the volume of data obtained in each study, the number of subjects in each of these three groups had to be kept relatively small. For the same reason it was thought best to use the standard therapeutic dose of morphine rather than attempt to study the effect at different dose levels for which larger numbers of subjects would have been needed.

METHODS

The haemodynamic changes consequent upon an intravenous injection of morphine sulphate were studied in three groups of subjects (Table 18).

Group I: Six normal subjects, each without any detectable abnormality likely to be of haemodynamic significance.

Group II: Four patients in left ventricular failure. None of these patients had valvular heart disease as judged by the previous history, absence of significant cardiac murmurs and subsequent course of the illness. The aetiological basis of left ventricular failure was either hypertension (two patients) or ischaemic heart disease (two patients), but none had suffered acute myocardial infarction. Clinical criteria for the diagnosis of acute left ventricular failure were: evidence of orthopnoea preceded by a history of frequent paroxysmal nocturnal dyspnoea, evidence of left

ventricular enlargement, a left-sided gallop rhythm, basal râles and in some cases a raised jugular venous pressure but without any hepatic enlargement or peripheral oedema. All had radiographic evidence of left ventricular enlargement and pulmonary oedema, and the electrocardiogram showed left ventricular enlargement and myocardial ischaemia. All patients were in sinus rhythm.

On clinical grounds, three patients (G.C., T.H., and A.S.) were considered to be in acute left ventricular failure at the time of the investigation, while the fourth patient (R.T.), who had similar evidence of acute left ventricular failure at the time of admission to the hospital, was no longer orthopnoeic by the time the investigation was commenced. A few hours rest in bed alone had resulted in an improvement in the clinical condition of this patient, but he still had a gallop rhythm and basal râles at the time of the study so that he was considered to be in "incipient" left ventricular failure. None had received digitalis, diuretics or morphine prior to the investigation. The laboratory was placed on a stand-by basis for these patients, the investigation being commenced as soon as the clinical diagnosis was established and the possibility of acute myocardial infarction excluded with the help of an electrocardiogram.

Group III: Four patients who had mitral valve disease of varying severity, but without clinical evidence of aortic valve disease. In three cases, mitral stenosis was considered to be the dominant lesion while in the fourth (L.C.) mitral incompetence was dominant. None of these patients had evidence of cardiac decompensation, although two patients (L.C. and M.R.) had been in congestive cardiac failure on previous occasions. Two patients were in sinus rhythm, while the other two were in atrial fibrillation.

All patients of groups I and III were studied in the supine position while patients of group II were kept propped up in a comfortable position. The postural difference was taken into account and appropriate corrections made in the pressure measurements.

The plan of investigation (Fig. 24) was identical in all patients. Normal subjects and patients with mitral valve disease were requested to perform light, non-fatiguing, supine leg exercise before the commencement of the definitive study. Following exercise, a recovery period of 15 minutes was allowed before control observations were recorded. This procedure has been shown to enable a relatively "steady state" to be attained rapidly (Donald et al, 1955). Patients of group II did not perform exercise for obvious reasons.

Control observations were made over a period of 10 minutes, following which the appropriate dose of morphine sulphate (15 mg./70 kg. body weight), diluted in 10 ml. of saline, was rapidly injected, over a period of 15 seconds, into the right atrium through the appropriate lumen of the quadruple lumen cardiac catheter. Further observations were then made over the succeeding 60 minutes.

Intravascular pressures and electrocardiogram were continuously recorded throughout the study. Dye curves were obtained at alternate minutes during the control period, at 1 and 2 minutes after the injection of morphine and at alternate minutes up to 10 minutes, following which these were recorded at 5 minute intervals. Samples of mixed venous blood were obtained while each dye curve was being transcribed. Arterial blood samples were obtained at intervals as shown in Fig. 24, and analysed for oxygen content, blood gas tensions, pH and blood sugar levels. Short strips of at least 10 aortic pressure pulses immediately

HAEMODYNAMIC EFFECTS OF INTRAVENOUS MORPHINE SULPHATE

EXPERIMENTAL DESIGN

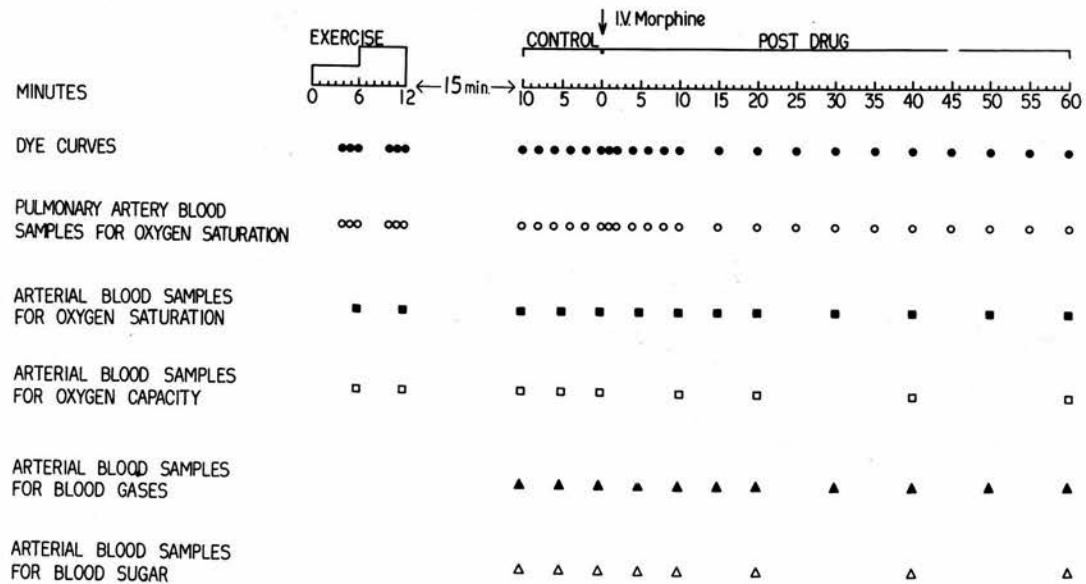


Figure 24

The experimental protocol used for studying the haemodynamic changes following an intravenous injection of morphine sulphate.

4. Period 4: from 45 to 60 minutes, both inclusive)

- delayed effects

This division into time periods is obviously entirely arbitrary.

Observations during the first 9 minutes after injection of morphine (post-drug period 1) were studied individually. Because of the transient nature of changes observed during this period averaging the data was not considered justifiable. Furthermore these changes, whenever present, were so marked that detailed statistical analyses were not considered necessary. The rest of the data was analysed as follows:

The mean and standard deviation of the individual values of each variable during the control period and during each of the three post-injection periods (2, 3 and 4) were calculated for each subject separately. The mean values of each variable during the various periods were then compared with each other (in each subject separately) by the "Student's" *t* test taking into account the differences between the respective variances of the means wherever these differences were demonstrated to be significant by the *F* test. Next in each of the three groups of patients a further analysis of the changes in each variable (during each time period) was carried out in the form of an analysis of variance. The details of the statistical procedures used are given in the appendix.

This form of statistical treatment, involving division into arbitrary time periods, can be criticised for failing to take into account the variable time course of changes in different subjects. Such a partitioning of data would, however, only result in making the present analysis less sensitive (by increasing the value of the variance) so that conclusions drawn would tend to err on the side of caution. Although the number of observations in each time period was small, which would

again tend to underestimate the level of probability, it is hoped that in this way any definite trends of change with respect to time would be identified. The only other approach that could have been employed is that of a time series analysis but on the basis of expert advice it was felt that little further information could be obtained by this method.

RESULTS

CLINICAL OBSERVATIONS

All patients noted flushing of the face and paraesthesiae, described as "tingling", followed by the same sensation over the upper limbs, trunk and lower limbs, in that order. At the same time, cutaneous hyperaemia was noted in all subjects. These features were observed within 15 seconds of the injection of morphine by subjects of groups I and III and, after a slightly longer interval, by those in group II. During this time most patients also complained of a throbbing headache which passed off rapidly. In some patients transient hyperventilation was observed during the first few minutes but no measurements of ventilation were made. Both subjective and objective changes were transient and passed off within 2 to 6 minutes, after which all subjects settled down and were calm throughout the rest of the procedure. Some subjects did feel drowsy but none of them actually slept. Patients of group II who were orthopnoeic felt more comfortable after about 15 to 20 minutes of the injection but none of them was allowed to change their posture while the study was in progress.

An interesting observation was that of orthostatic hypotension, invariably observed after completion of the study. This was associated with marked skin pallor, a feeling of giddiness, and nausea, while some subjects actually vomited. The syndrome could be reversed on regaining

the supine position and the subjects were further helped by mild supine leg exercise. Towards the later part of the present studies, the subjects were not allowed to assume a sitting or upright position for 1 to 2 hours after completion of the study, and in these no such symptoms were observed. One of the subjects in group II (T.H.) felt nauseated and vomited 45 minutes after injection of the drug (while the study was in progress) and the haemodynamic changes observed at this time will also be discussed.

All subjects were considered to be in a reasonably "steady state" throughout the study period on the basis of narrow fluctuations in the primary variables particularly during the control periods (Donald et al, 1954).

The control measurements of the various haemodynamic variables were in agreement with the clinical diagnoses in all subjects. Both the resting measurements and the response to supine leg exercise (latter performed before the commencement of the definitive study and data not included) were within the normal range in all six subjects of Group I. While the resting cardiac outputs in two of the four patients in group III were within the normal range, all showed an impaired response to supine leg exercise. Three patients had mild to moderate pulmonary hypertension. In the fourth patient the resting pulmonary artery and wedge pressures were normal but both increased markedly on exercise.

The four patients of group II showed haemodynamic evidence of left ventricular failure (Hayward, 1955; Louisada and Cardi, 1956; Fejfar et al, 1959; and Finlayson et al, 1961). The cardiac output was low in all cases and this was associated with a markedly increased systemic vascular resistance except in one patient (G.C.) who had a low mean aortic pressure and only slightly increased systemic vascular resistance. The three

patients who were considered to be in acute left ventricular failure also had a sinus tachycardia, increased pulmonary artery and wedge pressures, and increased pulmonary vascular resistance. The mean circulation time was prolonged. Although the resting oxygen uptake was within normal limits the A-V oxygen content difference was markedly increased. PO_2 was reduced but variable changes were seen in PCO_2 and pH. The fourth patient (R.T.) who was considered to be in "incipient" left ventricular failure also had a low cardiac output but the heart rate and pulmonary artery and wedge pressures were only marginally increased. Both the systemic and pulmonary vascular resistances were increased in this patient, and so was the A-V oxygen content difference. Blood gas tension (PO_2 and PCO_2) and pH were within normal limits in this patient. These haemodynamic changes would be consistent with impaired left ventricular function not amounting to pulmonary oedema. From the point of view of response to intravenous morphine this patient could not be distinguished from the rest of the patients of this group.

The sequential changes observed in individual subjects are presented in Tables 19 to 32. The data for each subject of groups I and II is presented in two Tables marked A and B (e.g. 19A and 19B) the former containing observations on systemic and pulmonary circulation and the latter more specific data on left ventricular performance. Subjects of group III have only one table since parameters of left ventricular performance were not measured in them (vide supra). A summary of the results of statistical analyses is given in Tables 33 to 42. The 5% level of probability has been accepted as indicating significant deviation from the null hypothesis. Percentage figures refer to changes from the average

of control observations.

A description of the results obtained follows:

Group I : Normal Subjects

Cardiac Output (Fig. 25 to 27) increased at 1 minute after the injection of morphine by an average of 27.3% (range 9.2% to 38.2%), and in all six subjects returned to control levels within 2 minutes (J.R., G.P., and J.C.), 4 minutes (P.S., and J.W.) or 8 minutes (M.W.). Later in three subjects (P.S., G.P., and J.C.) it continued to decrease further to levels below their respective control ranges while another two subjects (J.R., and M.W.) maintained their cardiac output within the range of control observations up to 20 and 25 minutes before showing a similar decrease. Thus in five subjects the cardiac output had stabilised at a level significantly below the range of control observations by 25 minutes after the injection of morphine (Table: 33). In the remaining subject (J.W.) the cardiac output increased after 25 minutes (Fig. 25), the average increase during 45 to 60 minutes (period 4) amounting to 11.6%.

The analysis of variance for the group as a whole demonstrated a highly significant decrease in cardiac output during periods 2, 3 and 4 (Table : 33), the average change amounting to 5.0%, 6.3% and 7.0% respectively. If subject J.W. is excluded from the analysis, the corresponding figures were 5.2%, 9.1% and 10.7%.

In subject P.S. the first dye curve after the injection of morphine was recorded at 2 minutes. She was the very first subject studied and it was not known at the time that marked haemodynamic changes occur so soon after administration of the drug. The rest of the experimental protocol was the same in this subject as in all others. However the results obtained

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE SYSTEMIC CIRCULATION IN

NORMAL SUBJECTS

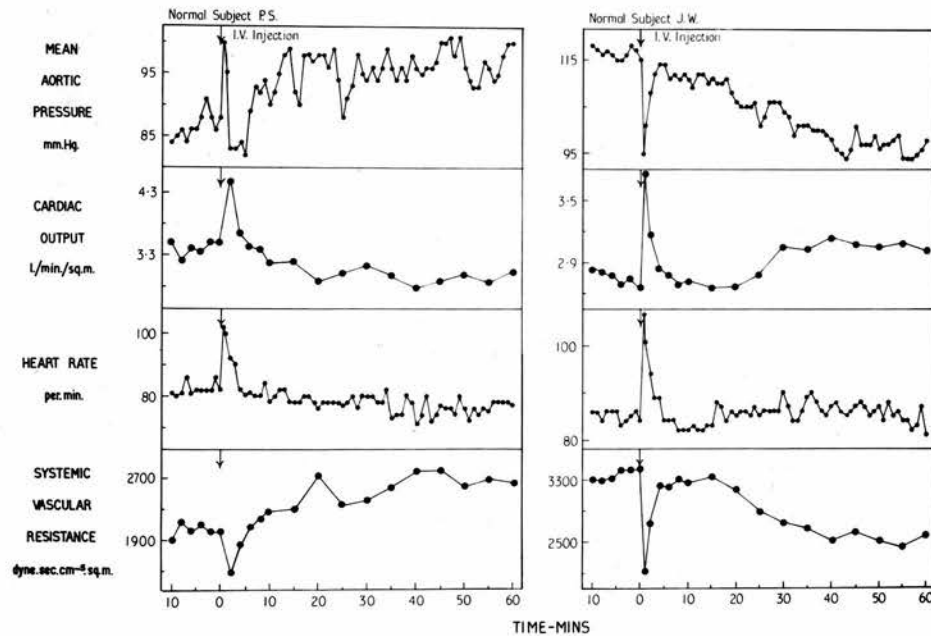


Figure 25

The sequential changes in systemic circulation before and after an intravenous injection of morphine sulphate in two normal subjects P.S. and J.W.

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE SYSTEMIC CIRCULATION IN
NORMAL SUBJECTS

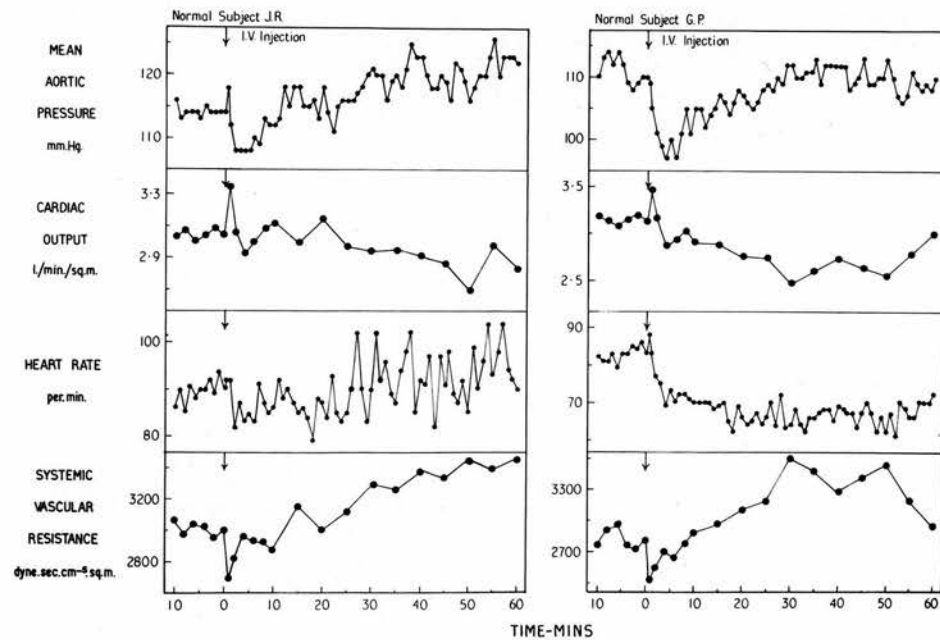


Figure 26

The sequential changes in systemic circulation before and after an intravenous injection of morphine sulphate in two normal subjects J.R. and G.P.

**EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE SYSTEMIC CIRCULATION
IN NORMAL SUBJECTS**

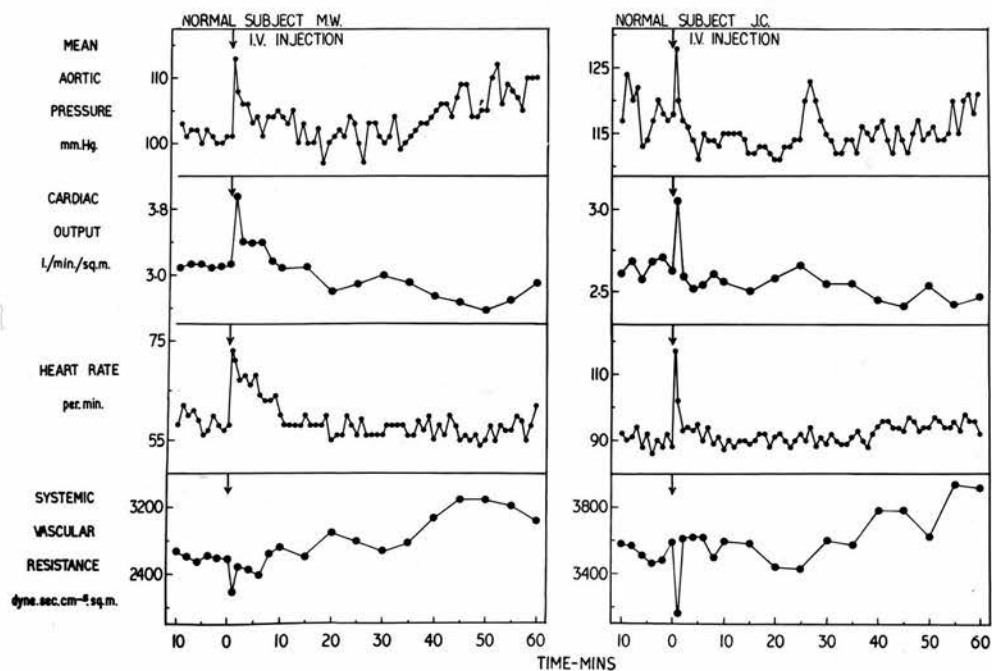


Figure 27

The sequential changes in systemic circulation before and after an intravenous injection of morphine sulphate in two normal subjects M.W. and J.C.

from this subject show that no material difference is made in the arguments as will be appreciated from the discussion.

Heart Rate (Figs. 25 to 27) increased immediately after the injection of morphine in five subjects, but rapidly returned to control levels within 1 to 10 minutes. The peak of this increase, ranging from 6.4% to 29.9% (average 19.9%) was observed at $\frac{1}{2}$ minute in four subjects (P.S., G.P., J.C., and M.W.) and at 1 minute in one subject (J.W.). Subsequently the heart rate decreased significantly in three subjects (P.S., G.P., and M.W.) while the other three showed a small increase which was statistically significant (Table: 33) only during period 3 in one subject (J.W.) and period 4 in two subjects (J.R. and J.C.). One subject (J.R.) developed a marked sinus arrhythmia which persisted throughout the study period.

The overall changes in heart rate during periods 2, 3 and 4 in this group revealed an average decrease of 4.7%, 3.7% and 2.8% respectively (Table: 33). These figures are weighted by the marked bradycardia observed in subject G.P., so that on excluding him from the analysis the corresponding figures revealed a decrease of only 2.0% and 0.4% during periods 2 and 3 while an increase of 0.5% was found during period 4.

Stroke Volume (Fig. 28) increased significantly at 1 minute in four subjects (P.S., J.W., G.P., and M.W.) returning to control levels within 2 to 4 minutes in all but one of them (G.P.). The other two subjects did not show any significant changes at this time. The average increase at 1 minute in all six subjects amounted to 8.6% (range 1.0% to 16.0%). In one subject (G.P.) the stroke volume remained elevated throughout most of the study period. Commencing between 15 and 25 minutes, a significant decrease in stroke volume was observed in four subjects (P.S., J.R., M.W., and J.C.) while the remaining one subject (J.W.) showed an increase.

**EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON STROKE VOLUME
IN NORMAL SUBJECTS**

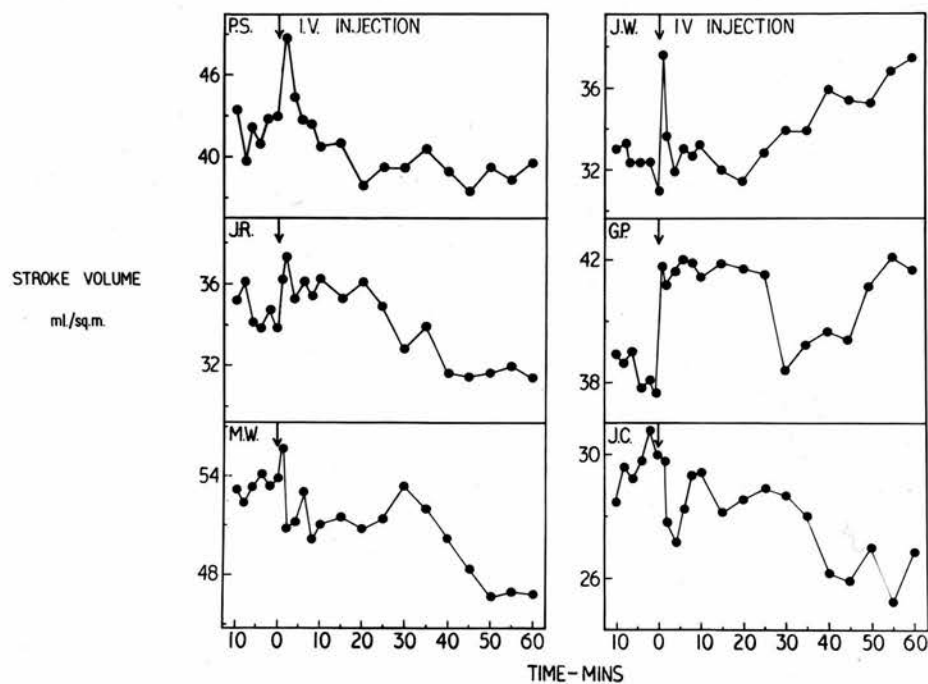


Figure 28

The sequential changes in stroke volume before and after an intravenous injection of morphine sulphate in six normal subjects.

The average change in the stroke volume in this group was a small but significant decrease amounting to 4.2% during period 4 only (Table: 33).

Mean Aortic Pressure (Figs. 25 to 27) increased significantly (between 3.1% and 15.3%) in four subjects (P.S., J.R., M.W., and J.C.) at $\frac{1}{2}$ minute, but at 1 minute this had returned to control levels in two of them (M.W. and J.C.), and even fallen below these levels in the other two (P.S. and J.R.). Another two subjects (J.W. and G.P.) had a rapid decrease in mean aortic pressure at this time, but in neither was a preceding increase observed. Thus in four of the six subjects the mean aortic pressure decreased after the injection of morphine, the lowest pressure (5.3% and 13.2%) of the control average being observed between $\frac{1}{2}$ and 4 minutes in individual subjects. However, in all subjects the pressure had returned to control levels within 5 to 15 minutes and after this further changes were variable. In three subjects (P.S., J.R. and M.W.) a small but significant increase (commencing at 6, 25, and 35 minutes respectively) was observed, while a decrease of similar order occurred in two subjects (G.P. and J.C.).

One subject (J.W.) showed a slightly different response in that the mean aortic pressure decreased markedly immediately after the injection of morphine but recovered rapidly only to decrease again, progressively but gradually, from 5 minutes onwards (Fig. 25). The average decrease, in this subject, during period 4 (45-60 minutes) amounted to 16.8%.

Results of the analysis of variance for the group did not show any consistent or significant changes between 10 and 60 minutes after the injection of morphine (Table: 33). During periods 2 and 3 average decreases of 1.0% and 0.5% respectively were observed, while an increase of 0.1%

occurred during period 4. The group averages are weighted by the marked decrease in the mean aortic pressure in subject J.W. If this subject be excluded from the analysis an average increase of 2.2% and 3.9% was found during periods 3 and 4 respectively.

Systemic Vascular Resistance (Figs. 25 to 27) decreased significantly at 1 minute by an average of 19.2% (range 10.5% to 37.3%) in all six subjects. Within 2 to 8 minutes the systemic vascular resistance was back within the range of control observations in all subjects. Later a gradual increase above the control levels (commencing between 10 and 40 minutes in individual subjects) was observed in five subjects (P.S., J.R., G.P., M.W., and J.C.) and this increase persisted throughout the rest of the study period in all but one subject (G.P.). In the sixth subject (J.W.) the calculated systemic vascular resistance decreased after 20 minutes stabilising at a level 25.0% less than the control average (period 4).

The analysis of variance for the group showed a highly significant increase amounting to 3.3%, 3.6% and 8.7% during periods 2, 3 and 4 respectively (Table: 33). If subject J.W. is excluded from the calculations, the average increase during these three periods amounted to 5.0%, 11.4% and 16.9% respectively.

The changes in systemic vascular resistance were thus generally similar in time sequence but opposite in direction to the changes in cardiac output in individual subjects (Figs. 25 to 27).

Oxygen Uptake (Fig. 29) increased significantly (14.5%) at the very first observation (2 minutes) after the injection of morphine in one subject (P.S.) but this had returned to control levels at 6 minutes. The small changes (increase in four and decrease in one) observed in the other five subjects at this time fell within two standard deviations of their

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON OXYGEN UPTAKE
IN NORMAL SUBJECTS

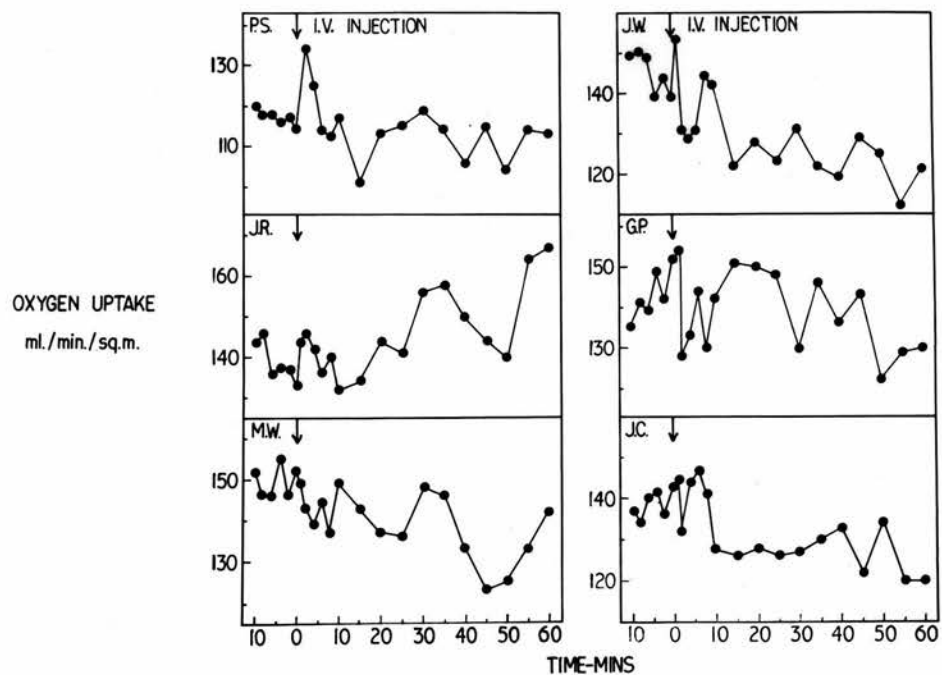


Figure 29

The sequential changes in oxygen uptake before and after an intravenous injection of morphine sulphate in six normal subjects.

respective control means and were not therefore significant. Later the oxygen uptake decreased in four subjects, the average decrease being statistically significant during periods 2, 3 and 4 in one subject (J.C.), periods 2 and 3 in another (J.W.), and only during period 4 in two subjects (G.P. and M.W.). An increase in oxygen uptake was observed in one subject (G.P.), but this was statistically significant during period 3 only. In subject P.S. the oxygen uptake remained within the range of control observations after the initial increase already referred to.

The analysis of variance revealed a highly significant decrease in oxygen uptake in this group (Table: 33). The average decrease during periods 2, 3 and 4 amounted to 4.3%, 4.3% and 7.2% respectively.

A significant narrowing (average 12.9%) of the A-V oxygen content difference was observed in all six subjects at 1 minute (Table:33) but later changes were variable. In two subjects (J.W. and J.C.) this narrowed significantly while in another three subjects (P.S., J.R. and G.P.) it increased. One subject (M.W.) did not show any significant change. Thus no significant overall change in the A-V oxygen content difference was seen in this group (Table: 33).

Mean Pulmonary Artery Pressure (Figs. 30 to 32) in one subject (M.W.) increased significantly (2.4 mm.Hg or 15.4%) but transiently at $\frac{1}{2}$ minute after the injection of morphine but returned to control levels by 3 minutes. The remaining five subjects did not show any significant changes at this time. Further changes were small and variable. One subject (P.S.) had a significant increase during periods 2 and 3, while another (J.W.) showed a decrease of similar magnitude at this time. In the remaining four subjects a tendency towards a decrease in the mean

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE PULMONARY CIRCULATION IN
NORMAL SUBJECTS

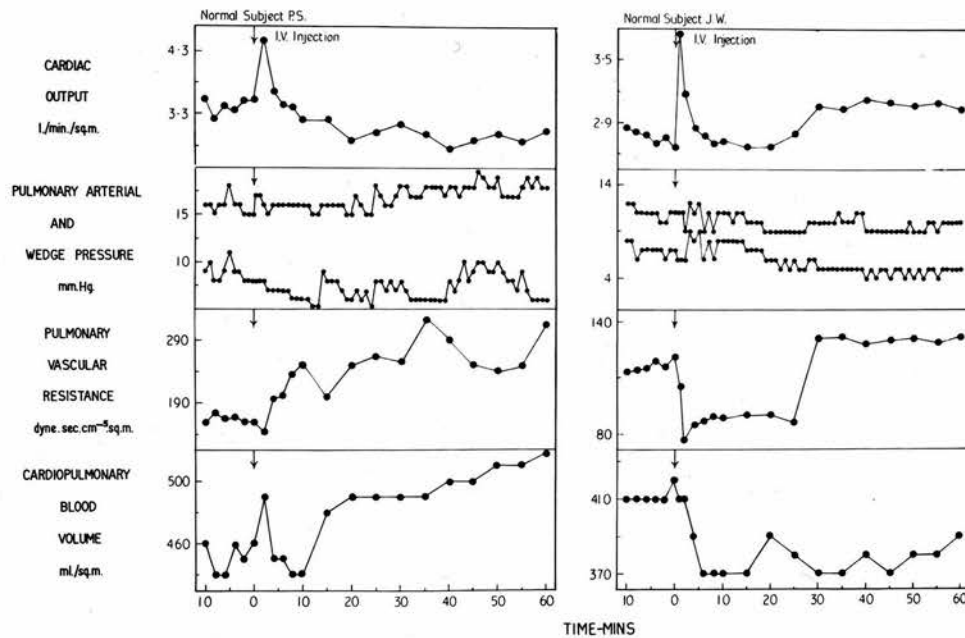


Figure 30

The sequential changes in pulmonary circulation before and after an intravenous injection of morphine sulphate in two normal subjects P.S. and J.W.

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE PULMONARY CIRCULATION IN
NORMAL SUBJECTS

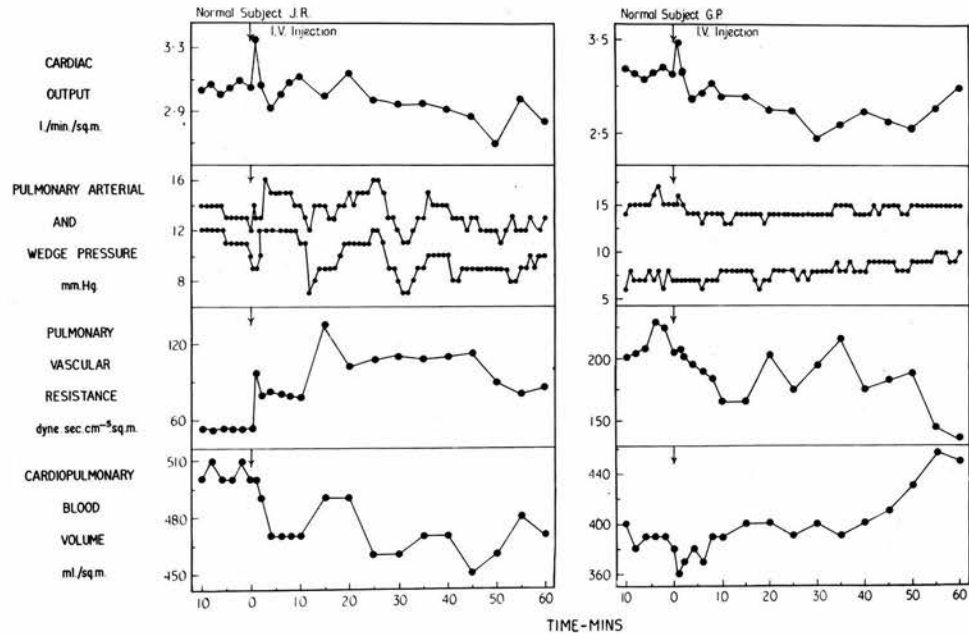


Figure 31

The sequential changes in pulmonary circulation before and after an intravenous injection of morphine sulphate in two normal subjects J.R. and G.P.

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE PULMONARY CIRCULATION
IN NORMAL SUBJECTS

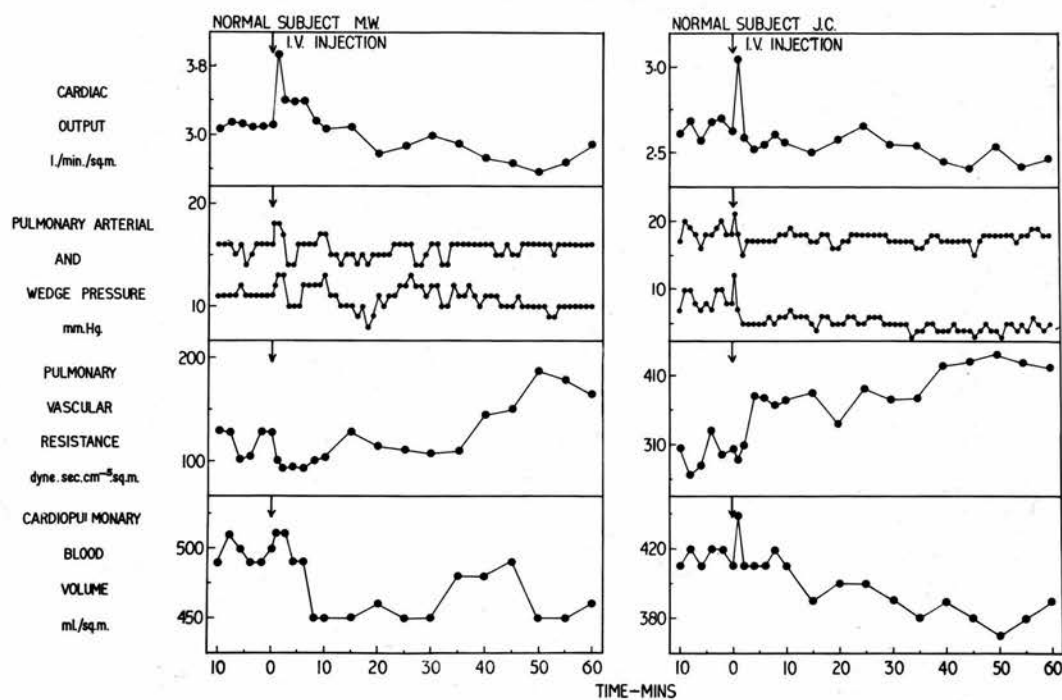


Table 32

The sequential changes in pulmonary circulation before and after an intravenous injection of morphine sulphate in two normal subjects M.W. and J.C.

pulmonary artery pressure was generally observed, but the average pressure changes were small in magnitude and achieved levels of significance at different time periods in different subjects (Table: 34). For the group the average pressures did not show any consistent or significant changes except for a small but significant decrease during period 2 only (Table:34).

Mean Pulmonary Wedge Pressure (Figs. 30 to 32) increased significantly (3.5 mm.Hg or 41.2%) at $\frac{1}{2}$ minute in one subject (J.C.), while in another subject (J.R.) a small reduction (2.4 mm.Hg or 21.1%) was observed at this time. In both subjects these changes were transient having reversed by 1 to 3 minutes. Later the mean pulmonary wedge pressure decreased below the control levels in five subjects and this was statistically highly significant during periods 2, 3 and 4 in two subjects (J.R. and J.C.), periods 2 and 3 in one subject (P.S.), periods 3 and 4 in one subject (J.W.), and period 4 in one subject (M.W.). The sixth subject (G.P.) increased his mean pulmonary wedge pressure significantly during periods 3 and 4.. For the group as a whole the analysis of variance showed a highly significant decrease in the average (mean) pulmonary wedge pressure during periods 2, 3 and 4 (Table:34). The magnitude of this reduction was 13.3%, 15.6% and 15.6% respectively. If subject G.P. (in whom the mean pulmonary wedge pressure increased) be excluded the average decrease in the remaining five subjects was 2 mm.Hg and the corresponding percentage decreases during periods 2, 3 and 4 were 16.0%, 20.2% and 23.4% respectively.

Pulmonary Vascular Resistance (Figs. 30 to 32) increased significantly in all but one (G.P.) subject. This increase commenced within the first four minutes in three subjects (P.S., J.R. and J.C.) while it became apparent after 30 minutes in one (J.W.) and 45 minutes in the other (M.W.) subject.

In one of these subjects (J.W.) a highly significant decrease, amounting to 23.3% was observed (between 1 and 25 minutes) prior to this increase (Fig. 30). The sixth subject (G.P.) showed a gradual decrease in this measurement throughout the study period.

For the group as a whole a highly significant increase in the average pulmonary vascular resistance during periods 2, 3 and 4 was shown by the analysis of variance (Table: 34). The magnitude of this increase was 13.1%, 26.3% and 30.0% respectively. If subject G.P. is excluded from the calculations an increase of 21.3%, 36.0% and 45.3% occurred during periods 2, 3 and 4 respectively.

Cardiopulmonary Blood Volume (Figs. 30 to 32) increased significantly but transiently at 1 minute only in two subjects (P.S. and J.C.) while in another subject (G.P.) a significant decrease was observed at this time. Later in four subjects (J.W., J.R., M.W. and J.C.) a significant and sustained reduction in the cardiopulmonary blood volume, commencing in different subjects between 2 and 15 minutes, was observed. The remaining two subjects (P.S. and G.P.) showed an increase in this measurement. The analysis of variance indicates a highly significant decrease in the cardiopulmonary blood volume (3.4% and 3.1%) during periods 2 and 3 in this group (Table: 34). The average decrease, after excluding the two subjects in whom an increase was seen, amounted to 6.5%, 7.2% and 7.7% respectively during periods 2, 3 and 4.

Mean Right Atrial Pressure (Fig. 33) decreased significantly in four subjects (J.W., G.P., J.C. and M.W.) within 2 minutes of the injection. This reduction in mean right atrial pressure persisted throughout the rest of the study in three subjects (J.W., G.P. and J.C.) while in the fourth subject the pressure tended to fluctuate at a level slightly below

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON RIGHT ATRIAL PRESSURE

IN NORMAL SUBJECTS

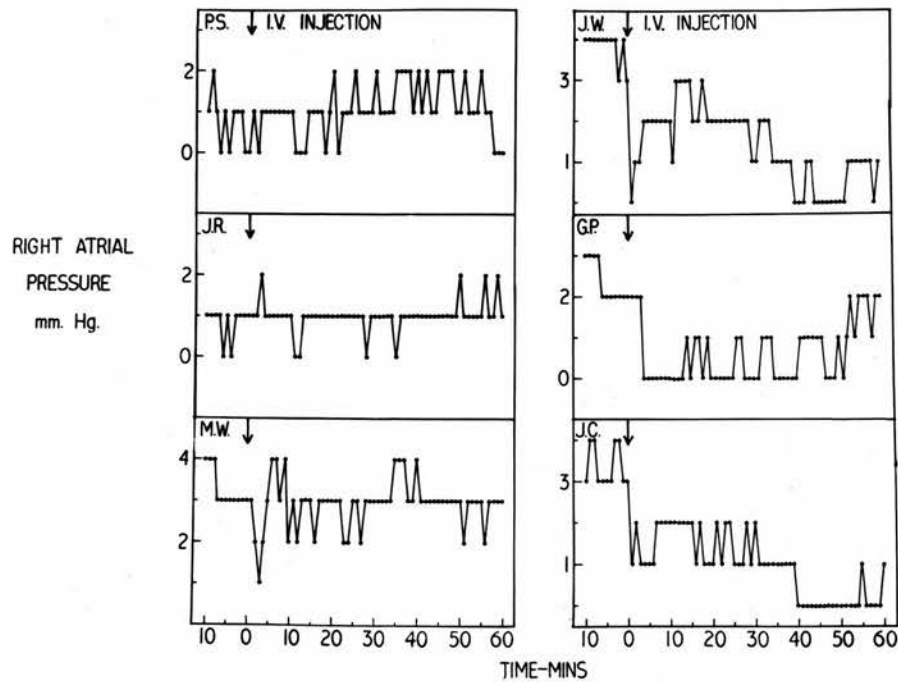


Figure 33

The sequential changes in mean right atrial pressure in six normal subjects.

the control mean (Table: 34). Another subject (P.S.) showed a marked increase during periods 3 and 4 while in the remaining one subject (J.R.) only a small increase was observed during period 4.

For the whole group an average decrease of 41.7%, 41.7% and 50.0% was observed during periods 2, 3 and 4 respectively. These changes were found to be statistically highly significant (Table: 34).

Mean Systolic Ejection Pressure (Tables:19B to 24B and 35) decreased significantly in all subjects, the lowest value being observed between 1 and 6 minutes in different subjects. Later this pressure returned to control levels in all subjects within 4 to 10 minutes. Subsequently a significant increase was observed during periods 2, 3 and 4 in one subject (P.S.), periods 3 and 4 in two subjects (J.R. and G.P.) and period 4 in one subject (M.W.). Of the remaining two subjects, one (J.W.) showed a significant decrease during periods 2, 3 and 4, while in the other (J.C.) a similar decrease was observed during periods 2 and 3. However, for the group as a whole, the changes during periods 2, 3 and 4 were not found to be significant by the analysis of variance (Table: 35).

Left Ventricular Stroke Work (Figs. 34 to 36) increased significantly but only transiently at 1 minute in three subjects (P.S., G.P. and M.W.). In one of these (M.W.) the mean pulmonary wedge pressure also increased at this time, while in the other two (P.S. and G.P.) this pressure remained within the control range. Both the left ventricular stroke work and mean pulmonary wedge pressure were within the range of control observations in two of the remaining three subjects at 1 minute, while in the third subject (J.R.) a small but significant decrease in the mean pulmonary wedge pressure without any significant change in left ventricular stroke work was observed.

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON LEFT VENTRICULAR PERFORMANCE IN NORMAL SUBJECTS

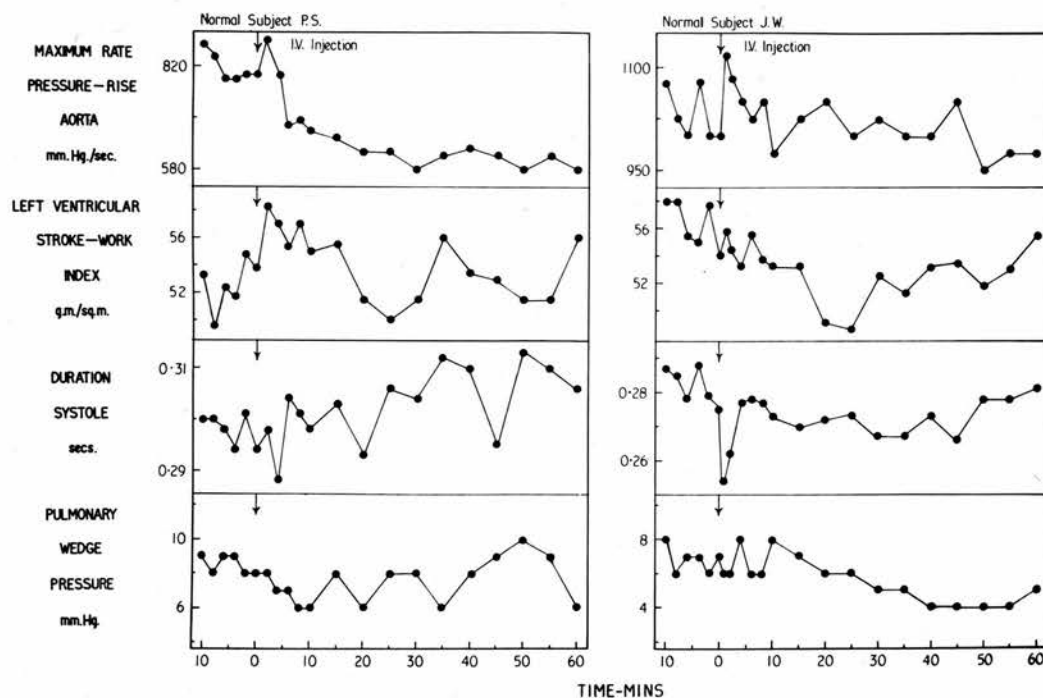


Figure 34

The sequential changes in some indices of left ventricular performance before and after an intravenous injection of morphine sulphate in two normal subjects P.S. and J.W.

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON LEFT VENTRICULAR PERFORMANCE

IN NORMAL SUBJECTS

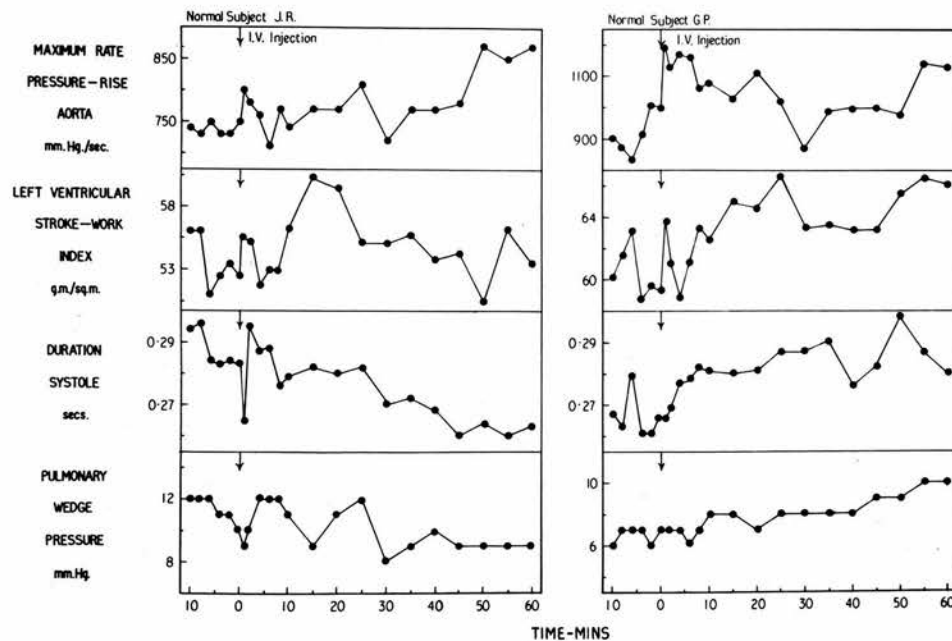


Figure 35

The sequential changes in some indices of left ventricular performance before and after an intravenous injection of morphine sulphate in two normal subjects J.R. and G.P.

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON LEFT VENTRICULAR PERFORMANCE IN NORMAL SUBJECTS

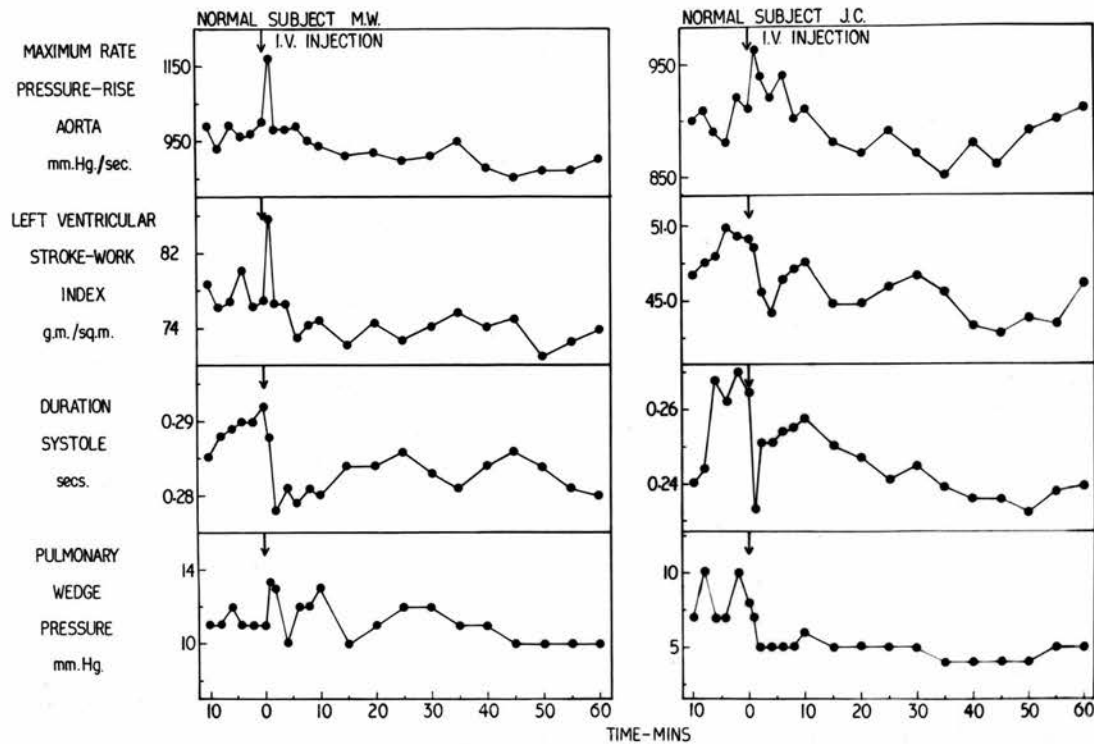


Figure 36

The sequential changes in some indices of left ventricular performance before and after an intravenous injection of morphine sulphate in two normal subjects M.W. and J.C.

Later the left ventricular stroke work decreased significantly during periods 2, 3 and 4 (10 to 60 minutes) in three subjects (J.W., M.W. and J.C.) and this was associated with a significant reduction in the mean pulmonary wedge pressure during periods 2, 3 and 4 in one subject (J.C.), periods 3 and 4 in another (J.W.) and period 4 only in the third (M.W.) (Table 35). In another subject (G.P.) both the left ventricular stroke work and the mean pulmonary wedge pressure increased significantly during periods 2, 3 and 4. The remaining two subjects (P.S. and J.R.) of this group did not show any significant changes in the left ventricular stroke work except for a small increase (9.3%) during period 2 in one of them (J.R.). In one of the latter two subjects (P.S.), a significant decrease in the mean pulmonary wedge pressure was observed during periods 2 and 3 while the other (J.R.) showed a similar change during periods 3 and 4.

The overall change between 10 and 60 minutes in these six subjects was a small but significant decrease in the left ventricular stroke work during periods 3 and 4 while the mean pulmonary wedge decreased significantly during periods 2, 3 and 4 (Table: 35).

Duration of Systole: (Figs. 34 to 36) changed inversely with the changes in heart rate. In three subjects (J.W., J.R. and J.C.), who increased their heart rate, the systolic cycle length was reduced, while in the two subjects (P.S. and G.P.) who developed a relative bradycardia, the duration of systole increased. However, in one subject (M.W.) a decrease in heart rate was associated with a decrease in the duration of systole. The overall change in the whole group was a small but significant decrease in the duration of systole during periods 3 and 4 (Table: 35).

Mean Stroke Power Index (Fig.37) increased at 1 minute by an average of 10.10% (range 5.3% to 12.9%) in all six subjects, but returned to control levels within 2 to 6 minutes in different subjects. Subsequent observations in four subjects (P.S., J. W., G.P., and J.C.) were generally

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON MEAN STROKE POWER INDEX
IN NORMAL SUBJECTS

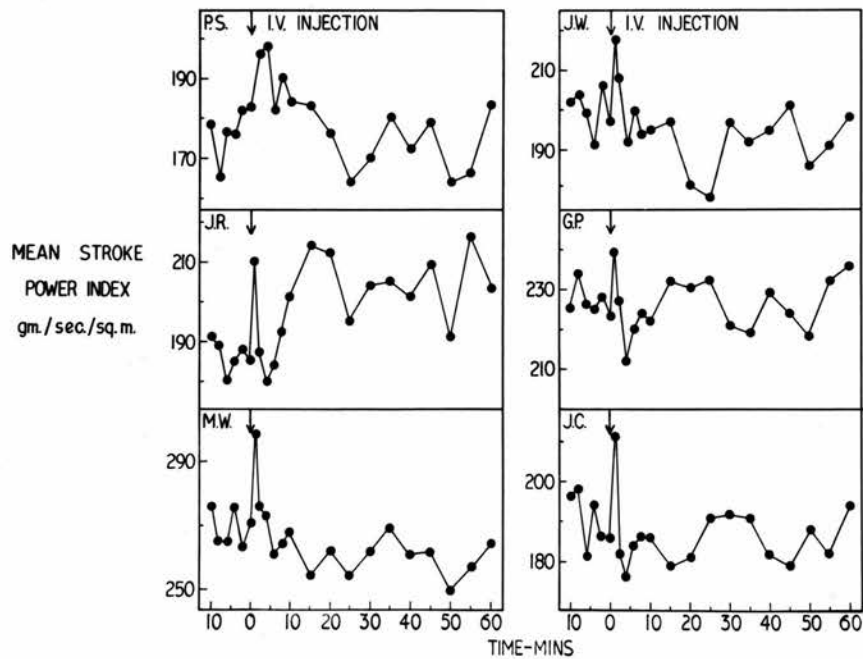


Figure 37

The sequential changes in mean stroke power index before and after an intravenous injection of morphine sulphate in six normal subjects.

within the range of control values throughout the study period. One subject (J.R.) showed a sustained increase in mean stroke power index during 10 to 60 minutes while a small but significant decrease was noted during period 4 (45 to 60 minutes) in another subject (M.W.). The analysis of variance did not reveal any significant changes in the average values of mean stroke power index during periods 2, 3 and 4 (Table: 35).

Mean Ejection Flow Index (Fig. 38) increased transiently at 1 minute by an average of 13.1% (range 5.4% to 28.7%) in all subjects. Later this had returned to control levels within 2 to 6 minutes in four subjects. In one of these (J.C.) no further changes were observed while a significant increase during periods 3 and 4 was seen in one (J.W.) and a similar decrease in another two (P.S. and M.W.). In the remaining two subjects (J.R. and G.P.) mean ejection flow index remained elevated (at a level lower than the initial increase) up to 20 minutes.

The overall changes in this group, between 10 and 60 minutes, revealed a small (2.0%) but significant decrease during period 4 only (Table: 35).

Maximum Rate of Pressure Rise in Aorta (Figs. 34 to 36) increased significantly at 1 minute in five of the six subjects (J.W., J.R., G.P., M. W., and J.C.), the average increase for the group being 16.1%. By 4 minutes this was again within the range of control observations in four of these five subjects, but remained elevated throughout the study period in the fifth subject (G.P.). Later, between 10 and 60 minutes, a significant decrease in dp/dt of the aortic pulse was observed in two subjects (P.S. and M.W.). One subject (J.W.) did not show any significant changes during this time, while a significant decrease was observed during period 3 in one

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON MEAN EJECTION FLOW INDEX
IN NORMAL SUBJECTS

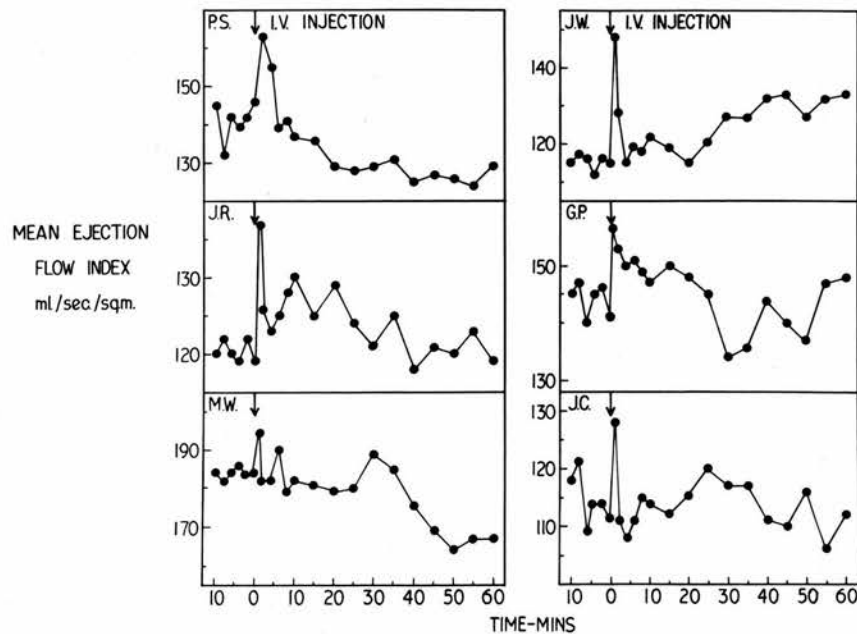


Figure 38

The sequential changes in mean ejection flow index before and after an intravenous injection of morphine sulphate in six normal subjects.

subject (J.C.), and another subject showed an increase during period 4 only (J.R.). The overall change in the whole group was a small but significant decrease during period 3 only (Table: 35).

Left Ventricular Minute Work (Figs. 39 to 41) increased significantly at 1 minute in all subjects by an average of 17.7% (range 6.8% to 34.1%). Subsequently it rapidly decreased so that within 2 to 15 minutes, in different subjects, the left ventricular minute work was below the respective ranges of control observations. Later it remained at this lower level in five subjects (P.S., J.W., G.P., M.W. and J.C.) while an increase above the control mean (7.1%) was observed between 10 and 20 minutes (period 2) in one subject (J.R.) only. The overall change in this group was a significant decrease (Table: 36) during periods 2, 3 and 4. The magnitude of the average change during these periods was 4.8%, 6.3% and 5.7% respectively. If subject J.R. is excluded from the analysis the corresponding figures were 7.2%, 8.2% and 7.4% respectively.

Mean Aortic Diastolic Pressure (Figs. 39 to 41) decreased significantly in five subjects (P.S., J.W., J.R., G.P. & M.W.). The lowest observed value was seen between 1 and 6 minutes in different subjects. Later this pressure had returned to control levels at 4 minutes in two (P.S. and J.W.), at 10 minutes in two (J.R. and M.W.) and at 25 minutes in one subject (G.P.). Subsequently in two (G.P. and M.W.) of these five subjects the mean aortic diastolic pressure remained within the range of control observations; an increase in this pressure was observed in two subjects (P.S. and J.R.); and one subject showed a progressive decrease (J.W.).

For the group as a whole the average (mean) aortic diastolic

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON SOME DETERMINANTS OF CORONARY BLOOD FLOW
IN NORMAL SUBJECTS

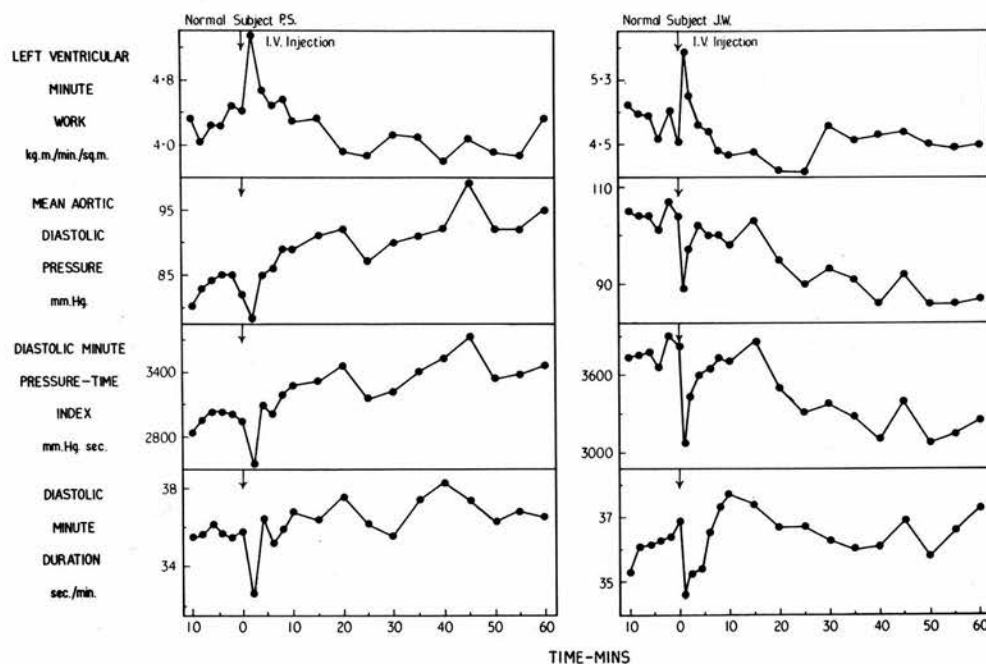


Figure 39

The sequential changes in some determinants of coronary blood flow before and after an intravenous injection of morphine sulphate in two normal subjects P.S. and J.W.

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON SOME DETERMINANTS OF CORONARY BLOOD FLOW

IN NORMAL SUBJECTS

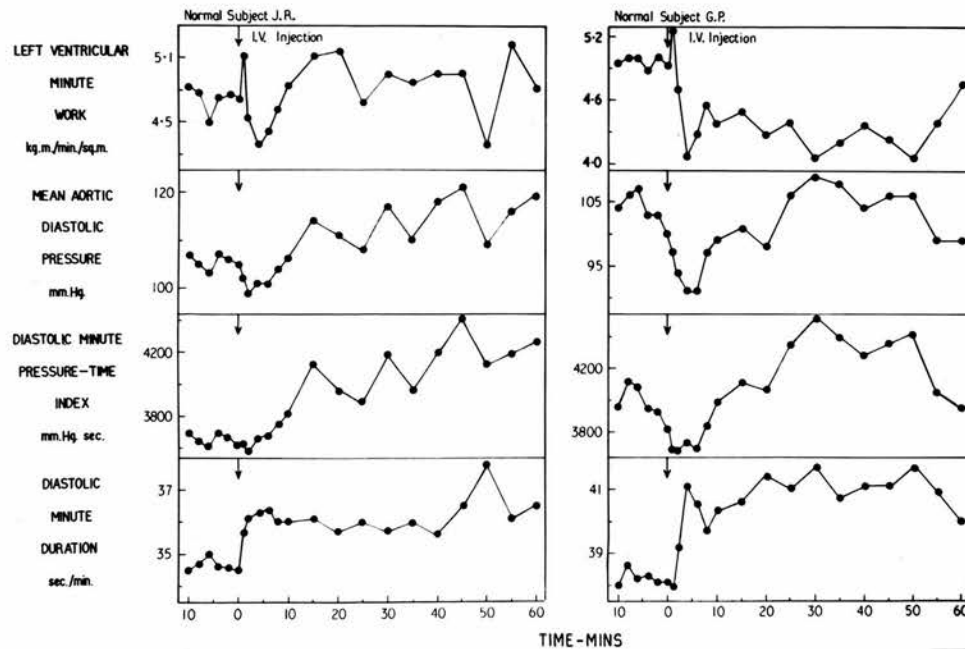


Figure 40

The sequential changes in some determinants of coronary blood flow before and after an intravenous injection of morphine sulphate in two normal subjects J.R. and G.P.

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE SOME DETERMINANTS OF CORONARY BLOOD FLOW IN NORMAL SUBJECTS

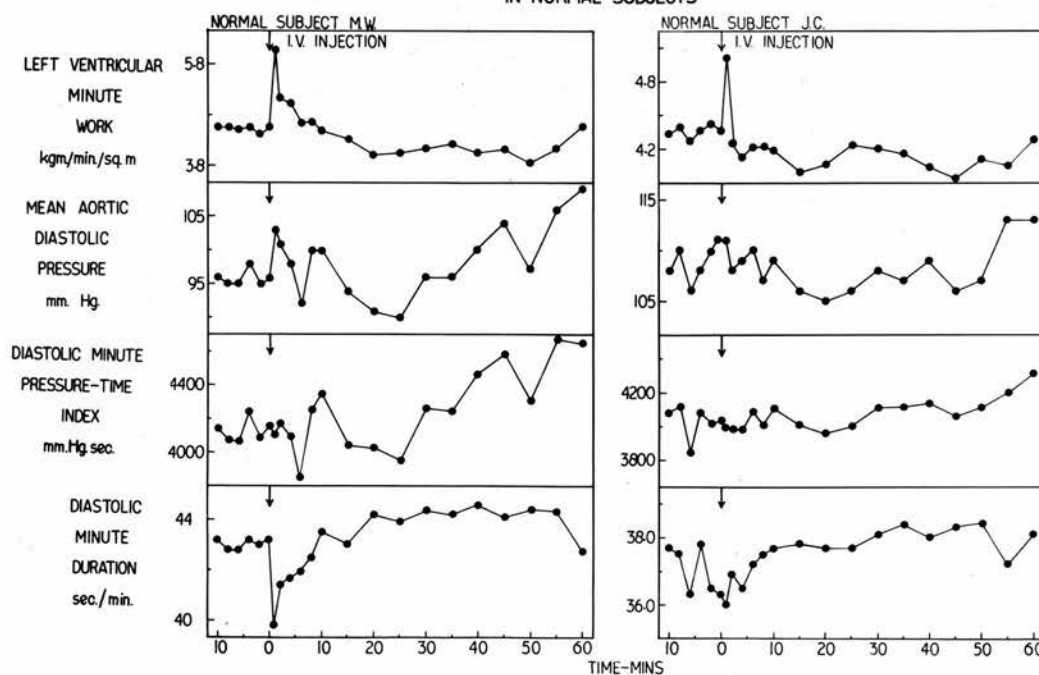


Figure 41

The sequential changes in some determinants of coronary blood flow before and after an intravenous injection of morphine sulphate in two normal subjects M.W. and J.C.

pressure during periods 2 and 3 was not significantly different from the mean of control observations while a small (2.3%) but significant increase was found during period 4 (Table: 36).

Duration of Diastole (Table: 36) per cycle generally changed inversely with the changes in heart rate. However the average diastolic minute duration (Figs. 39 to 41) during periods 2, 3 and 4 showed a small relative increase in all subjects. This was statistically significant during periods 2, 3 and 4 in two subjects (J.R. and G.P.), periods 3 and 4 in three subjects (P.S., M.W. and J.C.) and period 2 in one (J.W.) subject (Table: 36).

The overall change was a significant increase in both the diastolic cycle length and diastolic minute duration during periods 2, 3 and 4, the magnitude of the later increase being 8.1%, 9.2% and 8.1% respectively (Table: 36).

Diastolic Minute Pressure-Time Index (Figs. 39 to 41) decreased significantly in five subjects (P.S., J.W., J.R., G.P., and M.W.). The maximum decrease was observed between 1 and 6 minutes in different subjects, but within 2 to 8 minutes this was again within the range of control observations in each of them. Later a significant increase in this parameter was observed in four subjects (P.S., J.R., G.P. and M.W.), the average increase being significant during periods 2, 3 and 4 in one subject (P.S.), and during periods 3 and/or 4 in three subjects (J.R., G.P. and M.W.). One subject (J.W.) showed a significant decrease during periods 3 and 4. The remaining one subject (J.C.) did not show any significant changes throughout the study period.

The overall change was a significant increase as shown by the

analysis of variance, amounting to 3.1%, 3.8% and 6.0% during periods 2, 3 and 4 respectively (Table: 36). If subject J.W., (in whom the diastolic pressure decreased markedly), be excluded from the analysis the corresponding figures were 4.2%, 7.2% and 10.2% respectively.

Systolic Pressure-Time Index (Fig. 42) decreased initially in three subjects (J.W., J.R. and G.P.), the lowest observed value being noted between 1 and 4 minutes in different subjects. In two of these (J.W. and G.P.) the systolic pressure-time index was significantly below the mean of control observations throughout the study period while in the third subject (J.R.) it was within the range of such observations between 15 and 60 minutes. The remaining three subjects showed variable changes after the initial increase (significant in two : P.S. and M.W.) observed at 1 minute. The overall change for the group as a whole was a significant decrease during periods 2, 3 and 4 amounting to 5.5%, 5.8% and 4.2% respectively (Table: 36).

Group II: Left Ventricular Failure Patients

One of the four patients in this group (T.H.) vomited at 45 minutes after the injection of morphine. Additional dye curves were therefore recorded in this subject at 47 and 53 minutes (Table:26B). For purposes of statistical comparison only the observations made between 50 and 60 minutes were included in period 4. However, with the additional measurements made at 53 minutes the total number of available observations (except for vascular pressures and heart rate) during this period were the same as in the other patients. The analysis of variance test was carried out twice; once including the figures of period 4 from this patient and again after excluding these values. The final answer on both occasions was similar so

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON SYSTOLIC MINUTE PRESSURE-TIME INDEX IN NORMAL SUBJECTS

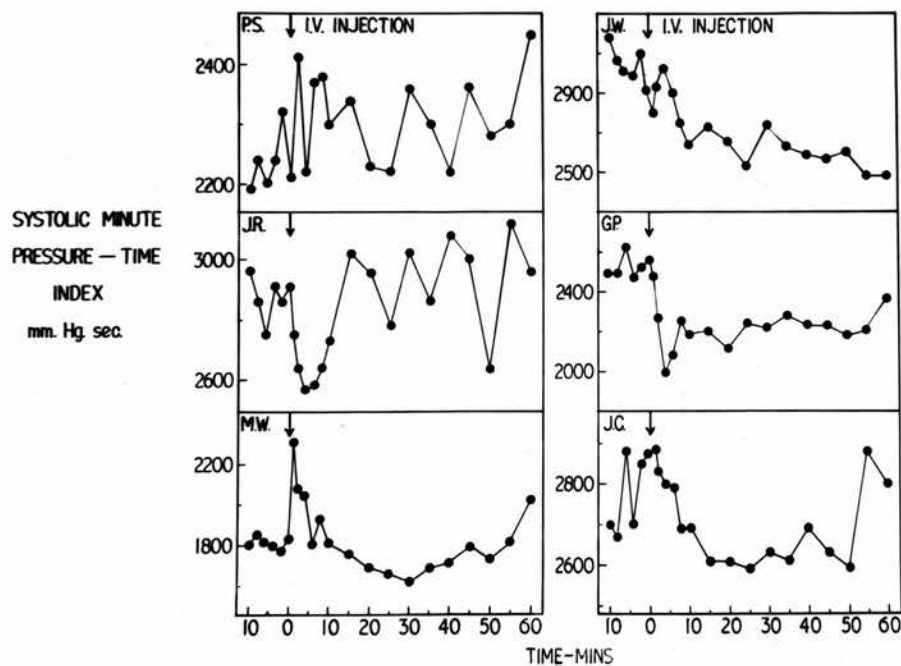


Figure 42

The sequential changes in systolic minute pressure-time index before and after an intravenous injection of morphine sulphate in six normal subjects.

that no further account has been taken of the latter results.

Cardiac Output (Figs. 43 and 44) decreased in two patients (A.S., and R.T.) after the injection of morphine, the lowest values, amounting to a decrease of 17.2% and 9.8% of the control observations, being observed at 4 and 8 minutes respectively. In one of these two patients (A.S.) the cardiac output remained below the range of control observation for most of the study period (Fig. 44), but gradually increased to control levels during the last 15 minutes (period 4). The oxygen uptake in this patient had increased significantly (9.9%) at 2 minutes but later showed a persistent decrease between 4 and 60 minutes (Fig. 46). In the other patient (R.T.) the cardiac output was back within the range of control observations at 15 minutes and later even showed a small but significant increase (2.4%) during period 3 (Fig. 44) in spite of a significant decrease in oxygen uptake between 26 and 60 minutes (Fig. 46). Of the remaining two patients, one (G.C.) increased his cardiac output immediately after the injection of morphine, the maximum increase (amounting to 16.6%) being observed at 2 minutes, following which it decreased again but stabilised at a level significantly higher than the mean of control figures (Fig. 43). In the fourth patient (T.H.) no significant change was seen initially but the cardiac output decreased significantly after 10 minutes (Fig. 43).

The overall changes in the average cardiac output during periods 2, 3 and 4 was a small decrease which the analysis of variance showed to be not significant (Table: 37).

Heart Rate (Figs. 43 and 44) increased in two patients initially (G.C. and A.S.). The maximum observed increase (amounting to 4.2% and 5.6%) occurred at 4 and 8 minutes respectively. Later in one of these two subjects (G.C.) the heart rate decreased rapidly so that after 4 minutes

**EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE SYSTEMIC CIRCULATION IN
PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE**

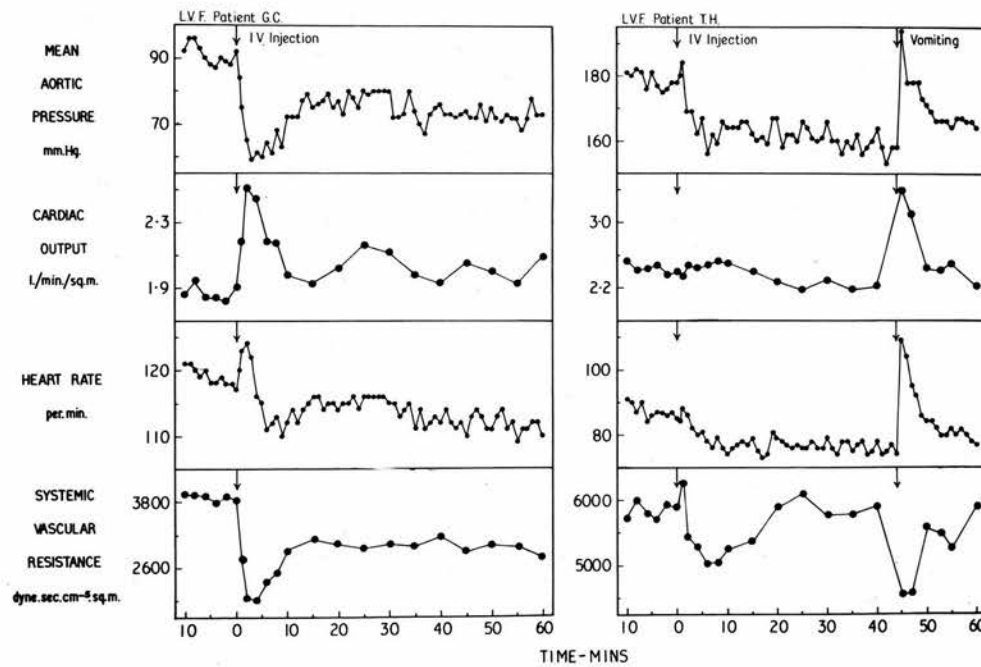


Figure 43

The sequential changes in systemic circulation before and after an intravenous injection of morphine sulphate in two patients with left ventricular failure G.C. and T.H.

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE SYSTEMIC CIRCULATION IN

PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE

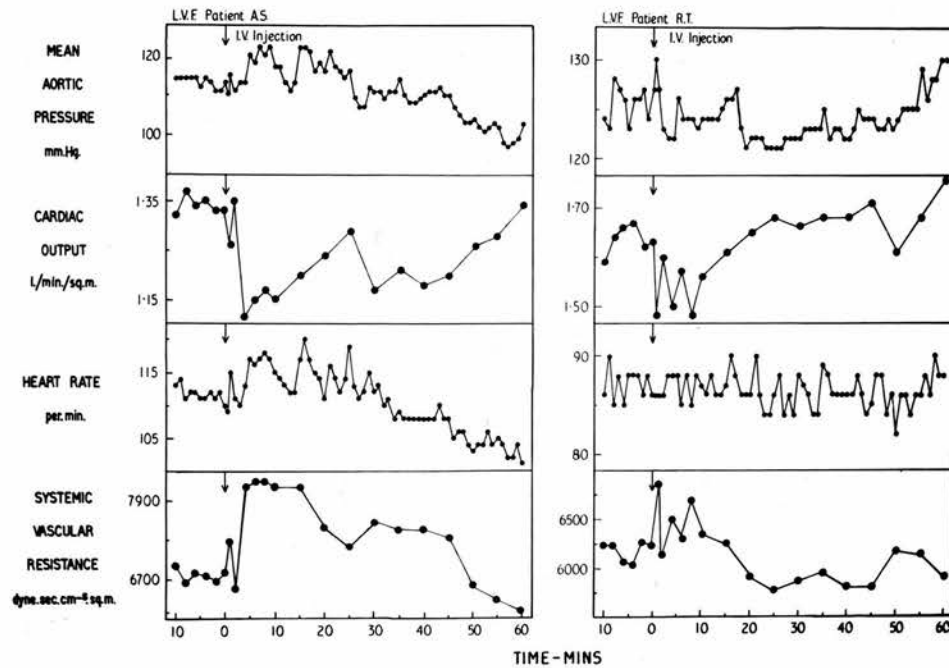


Figure 44

The sequential changes in systemic circulation before and after an intravenous injection of morphine sulphate in two patients with left ventricular failure A.S. and R.T.

it was below the control range and remained so throughout the rest of the study period (Fig. 43), the average decrease during periods 2, 3 and 4 amounting to 3.9%, 4.1% and 6.1% respectively (Table:37). Subject A.S., on the other hand, maintained the heart rate at a higher level up to 30 minutes, after which it progressively decreased to levels below the control range (Fig. 44). Of the remaining two subjects, one (R.T.) did not show any significant changes in the heart rate throughout the study period (Fig.44), while in the other subject (T.H.) a significant decrease commencing at 4 minutes (Fig. 43) and amounting to 12.3% and 12.4% during periods 2 and 3 respectively (Table:37) was observed.

For the group as a whole, the decrease in average heart rates during periods 2, 3 and 4 amounting to 3.2%, 4.3% and 4.1% respectively, was found to be significant by the analysis of variance test (Table: 37).

Stroke Volume (Fig. 45) showed a variable change, increasing initially in two patients (G.C. and T.H.) and decreasing in the other two (A.S. and R.T.) at this time. Later patient G.C. maintained his stroke volume significantly above the range of control observations, though at a level less than the initial increase, while in patient A.S. it remained lower than the control range up to 50 minutes. In the other two patients (T.H. and R.T.) the stroke volume was within the range of control observations during periods 2 and 3, while a small but significant increase was observed during period 4 in both of them (Table: 37).

The overall change for the group was a significant increase in stroke volume amounting to 2.7%, 1.6% and 6.4% during periods 2, 3 and 4 respectively (Table: 37).

Mean Aortic Pressure (Figs. 43 and 44) decreased rapidly after the injection of morphine in three patients (G.C., T.H. and R.T.) and remained

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON STROKE VOLUME

IN PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE

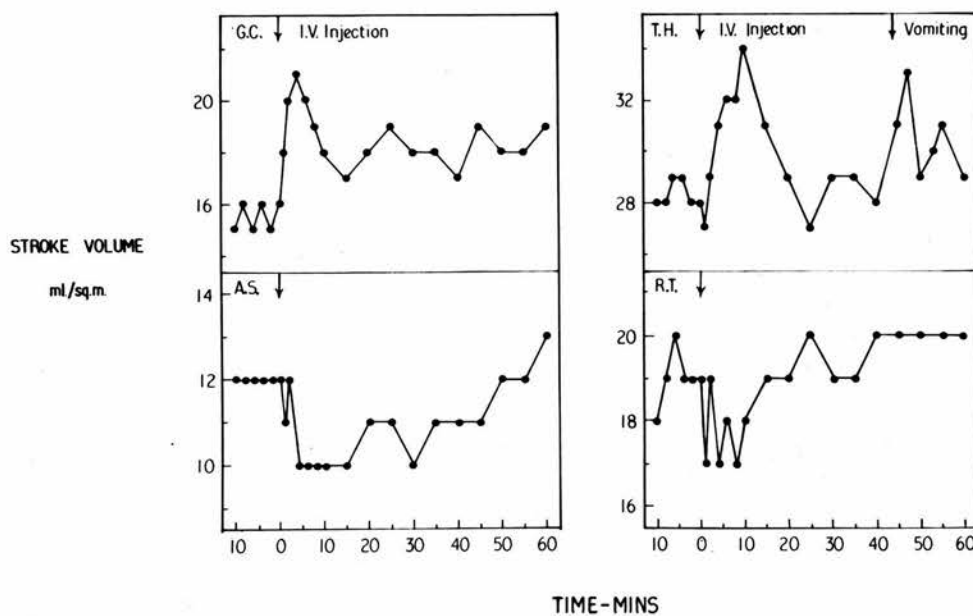


Figure 45

The sequential changes in stroke volume before and after an intravenous injection of morphine sulphate in four patients with left ventricular failure.

significantly below the mean of control observations throughout the study period except in one patient (R.T.) in whom it increased to control levels after 50 minutes. In the remaining patient (A.S.) the mean aortic pressure increased initially and remained elevated up to 20 minutes, after which it decreased below the control range.

The average change in mean aortic pressure during periods 2, 3 and 4 was a significant decrease amounting to 5.5%, 7.7% and 7.2% respectively (Table: 37).

Systemic Vascular Resistance (Figs. 43 and 44) increased significantly at 1 minute in three patients (T.H., A.S. and R.T.) by amounts ranging between 7.2% and 11.0%. Later in one of these three patients (A.S.) the systemic vascular resistance increased further (21.3% at 6 and 8 minutes) before declining gradually (15 minutes onwards) to control figures (Fig. 44). In the other two patients (T.H. and R.T.) the initial increase was followed by a decrease in this measurement to levels below the range of control observations (within 2 and 20 minutes respectively). The remaining patient (G.C.) showed a decrease in systemic vascular resistance at 1 minute which persisted throughout the study period (Fig. 43).

For the group as a whole, the average change was a significant decrease during periods 3 and 4 amounting to 2.1% and 7.1% respectively (Table: 37).

Oxygen Uptake (Fig. 46) increased initially (1 to 6 minutes) in three patients (G.C., T.H. and A.S.). Later it decreased gradually in two of these three patients, returning to control levels after 10 minutes in one patient (T.H.) and after 30 minutes in another (G.C.). In the third patient (A.S.) a more rapid decline in oxygen uptake was observed so that by 4 minutes it was below the range of control observations and remained

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON OXYGEN UPTAKE ON PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE

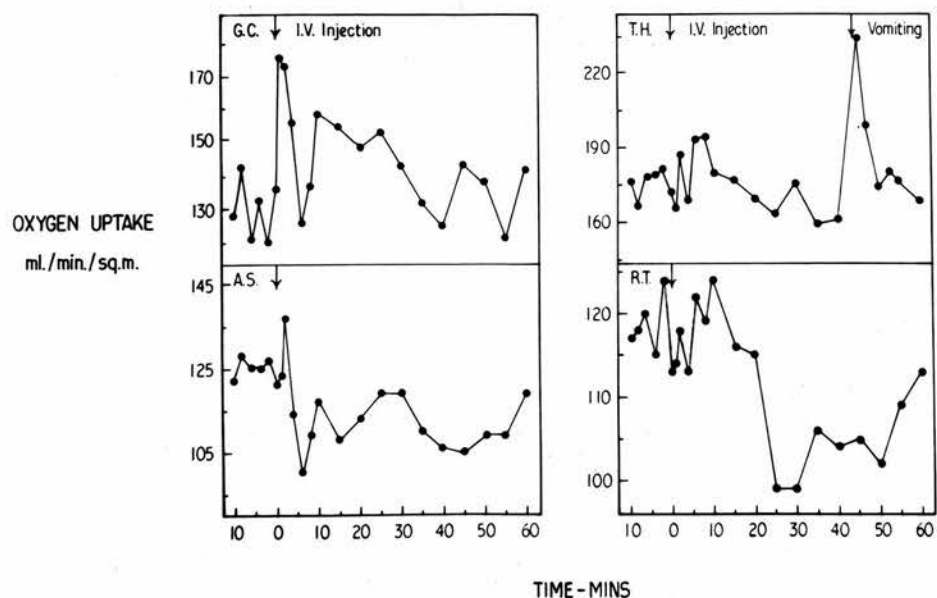


Figure 46

The sequential changes in oxygen uptake before and after an intravenous injection of morphine sulphate in four patients with left ventricular failure.

at a low level throughout the rest of the study period. In the remaining patient (R.T.) no consistent changes were seen up to 20 minutes, after which the oxygen uptake decreased significantly. For the group the average oxygen uptake during periods 3 and 4 showed a small but significant decrease amounting to 5.1% and 2.9% respectively (Table: 37).

The A-V oxygen content difference widened initially at 1 and/or 2 minutes in two (G.C. and A.S.) of the three patients in whom an increase in oxygen uptake was observed at this time. In one patient (G.C.) this increase in A-V oxygen content difference was observed in spite of an increase in cardiac output. No significant changes were seen in one patient (T.H.) throughout the study period, while in the remaining two patients (A.S. and R.T.) a significant narrowing of the A-V oxygen content difference was observed during periods 3 and/or 4. The overall average change during periods 2, 3 and 4 was a small but significant increase of 4.2% during period 2, while a significant decrease of 3.4% and 5.2% was found during periods 3 and 4 respectively (Table: 37).

Mean Pulmonary Artery Pressure (Figs. 47 and 48) decreased gradually in three patients (G.C., T.H. and R.T.) after the injection of morphine and remained below the control values throughout the study period, in all of them. The fourth patient (A.S.) increased his mean pulmonary artery pressure between 4 and 25 minutes, after which it remained within the range of control observations. During periods 2, 3 and 4 in this group, the average change amounting to 5.0%, 8.9% and 8.5% respectively was found to be highly significant by the analysis of variance (Table:38).

Mean Pulmonary Wedge Pressure (Figs. 47 and 48) decreased in all four patients. This was observed immediately after the injection of morphine

**EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE PULMONARY CIRCULATION IN
PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE**

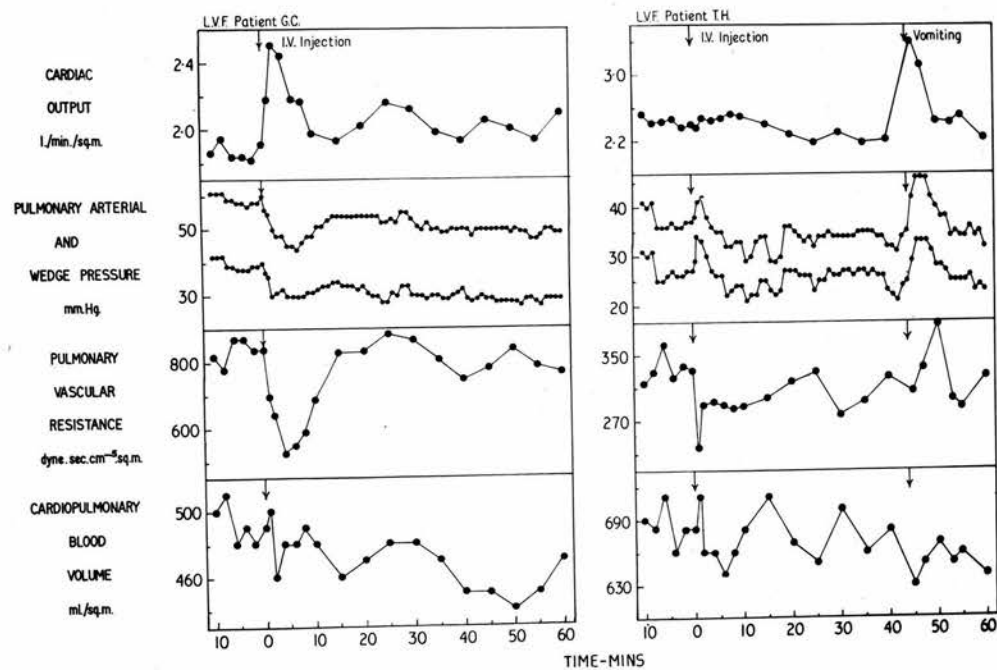


Figure 47

The sequential changes in pulmonary circulation before and after an intravenous injection of morphine sulphate in two patients with left ventricular failure G.C. and T.H.

**EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE PULMONARY CIRCULATION IN
PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE**

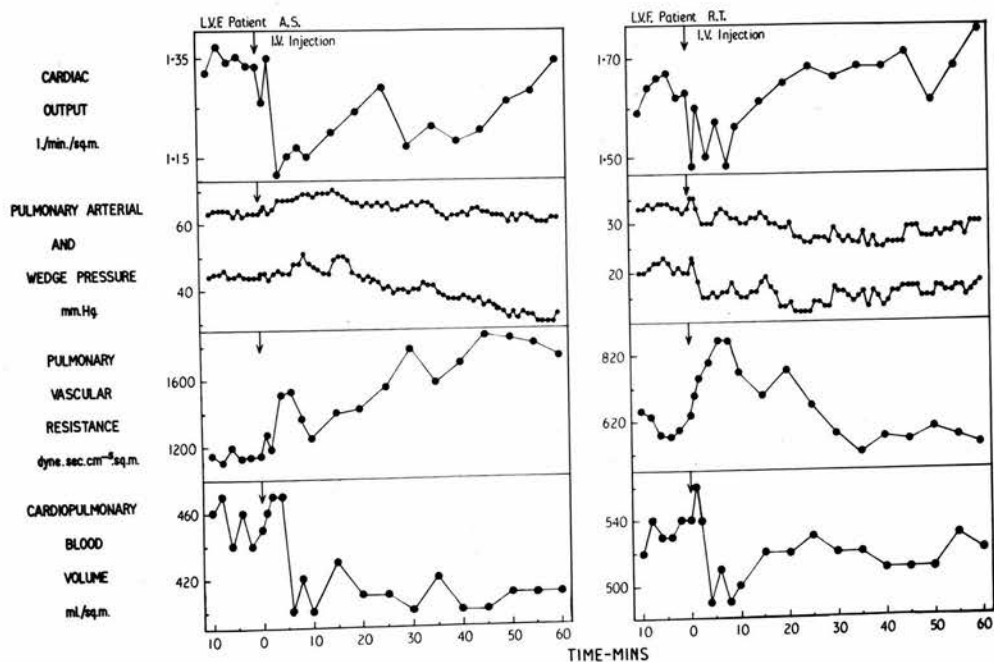


Figure 48

The sequential changes in pulmonary circulation before and after an intravenous injection of morphine sulphate in two patients with left ventricular failure A.S. and R.T.

in two patients (G.C. and R.T.), while in the other two a similar change was noted after 6 minutes (T.H.) and 18 minutes (A.S.). In one of these patients only (T.H.) a small but significant increase preceding these changes, was observed during the first 2 minutes (Fig. 47).

For the group as a whole the average decrease during periods 2, 3 and 4 amounted to 9.7%, 16.9% and 21.1% respectively. By the analysis of variance these changes were shown to be highly significant (Table: 38).

Pulmonary Vascular Resistance (Figs. 47 and 48) showed a variable change. In one patient (G.C.) an initial decrease was observed during the first 10 minutes, after which the pulmonary vascular resistance remained within the range of control observations (Fig. 47). Another patient (T.H.) also showed an initial decrease but in this case the pulmonary vascular resistance remained at a level lower than the control range throughout most of the study period (Fig. 47). The third patient (A.S.) showed a progressive increase after the injection of morphine, while in the fourth patient (R.T.) a similar increase was observed between 11 and 25 minutes, after which a small but significant decrease, as compared with the control mean, was noted (Fig. 48).

The overall change in pulmonary vascular resistance was a significant increase of 9.0%, 15.3% and 19.7% during periods 2, 3 and 4 (Table: 38). These figures are, however, weighted by the marked increase observed in one patient (A.S.) and on excluding him from the analysis an average increase amounting to 2.9% was found during period 2 only while in periods 3 and 4 the average change was a decrease of 3.4% and 5.2% respectively.

Cardiopulmonary Blood Volume (Figs. 47 and 48) decreased within 2 to 4 minutes after the injection of morphine in three patients (G.C., A.S.

and R.T.) and subsequently remained significantly below the range of control observations in all of them. In the fourth patient (T.H.) no consistent changes were seen up to 40 minutes, but a small (4.1%) but significant average decrease was observed between 50 and 60 minutes (period 4). The average change during periods 2, 3 and 4 was a small but highly significant decrease amounting to 3.5%, 4.1% and 5.7% during periods 2, 3 and 4 respectively (Table: 38).

Mean Right Atrial Pressure (Fig. 49) showed a variable change.

No significant changes were seen throughout the study period in two patients (T.H. and R.T.). In one patient (G.C.) a persistent decrease, commencing immediately after the injection of morphine, was observed, while in another patient (A.S.) a significant increase was observed during the first 30 minutes, after which the mean right atrial pressure returned to control levels. The average change in this group was an increase of 4.4% during period 2 and a decrease of 9.9% and 6.6% during periods 3 and 4 respectively. The latter changes were found to be statistically significant (Table: 38).

Mean Systolic Ejection Pressure (Tables 25B to 28B and 39) decreased significantly in two patients (G.C. and T.H.) within 2 minutes of the injection of morphine and subsequently remained below the range of control observations throughout the study period. In another patient (R.T.) a similar decrease, commencing at 2 minutes, was noted, but during periods 2 and 4 the average figures were not significantly different from the control observations. In the fourth patient (A.S.) this pressure remained at control levels up to 35 minutes, after which a significant decrease was noted. Thus during periods 2, 3 and 4, in this group, a significant decrease amounting to an average of 6.7%, 7.1% and 7.6% respectively was observed (Table: 39).

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON RIGHT ATRIAL PRESSURE IN
PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE

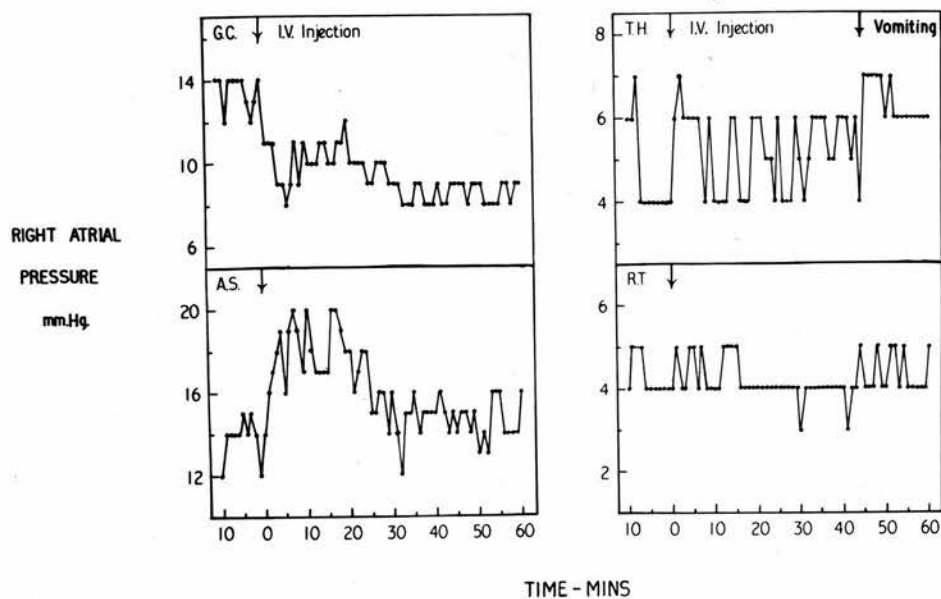


Figure 49

The sequential changes in mean right atrial pressure before and after an intravenous injection of morphine sulphate in four patients with left ventricular failure.

Left Ventricular Stroke Work (Figs. 50 and 51) decreased immediately after the injection of morphine in all four patients and the maximum decrease of between 6.0% and 20.4% was observed within 4 minutes. Subsequently the left ventricular stroke work gradually increased so that it was within the range of control observations after 10, 25 and 50 minutes in patients R.T., G.C. and A.S. respectively. In the fourth patient (T.H.) the initial decrease was followed by a return to control levels for a brief period (4 to 10 minutes) after which it decreased again.

In this group the overall changes in left ventricular stroke work during periods 2 and 3 were small but significant decreases amounting to 3.7% and 4.0% respectively. During period 4, a small increase (2.2%) was observed but this was not statistically significant (Table: 39).

The changes in left ventricular stroke work in these patients were associated with a decrease in the mean pulmonary wedge pressure except in one subject (T.H.) in whom there was an initial increase in the mean pulmonary wedge pressure during the first 2 minutes, and another subject (A.S.) in whom a similar increase was observed between 4 and 10 minutes, at a time when the left ventricular stroke work had decreased.

Duration of Systole (Figs. 50 and 51) generally followed the changes in heart rate, increasing when the heart rate decreased and vice versa. However, in one patient (R.T.), in whom the heart rate did not show any significant changes, the duration of systole decreased during periods 2 and 3. The average duration of systole during periods 2 and 3 in the whole group was, however, not significantly different from the control values, whereas during period 4 a small (3.1%) but significant increase was observed (Table: 39).

**EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON LEFT VENTRICULAR PERFORMANCE
IN PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE**

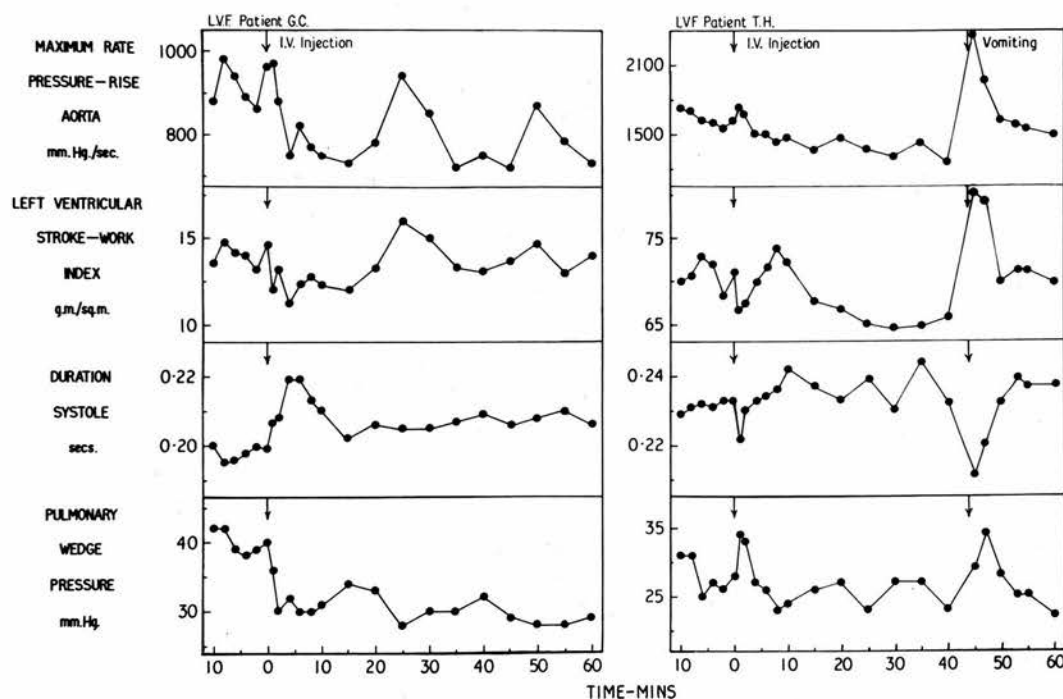


Figure 50

The sequential changes in some indices of left ventricular performance before and after an intravenous injection of morphine sulphate in two patients with left ventricular failure G.C. and T.H.

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON LEFT VENTRICULAR PERFORMANCE

IN PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE

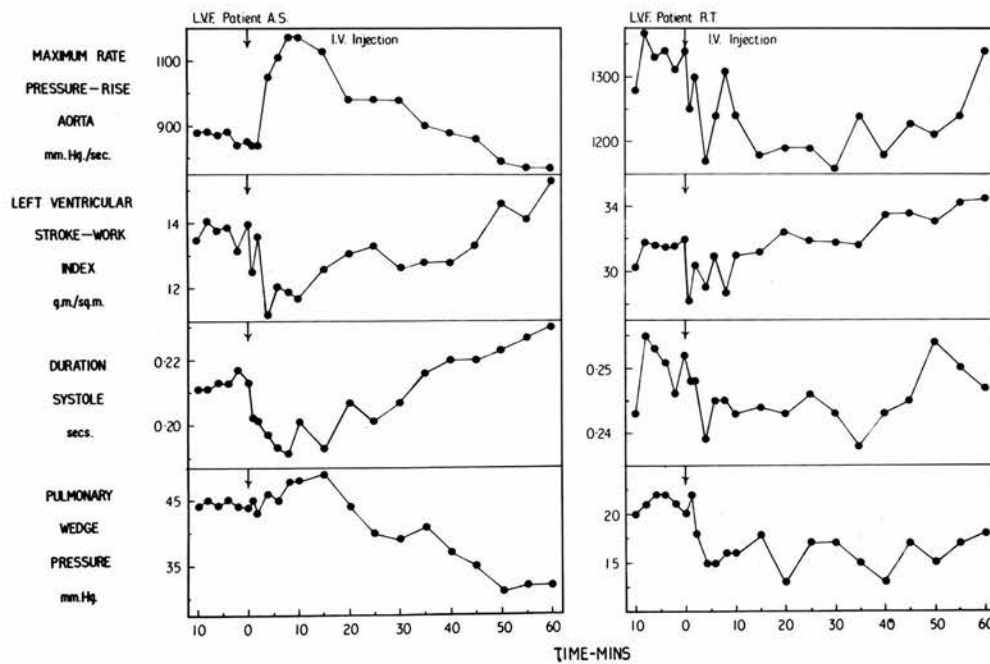


Figure 51

The sequential changes in some indices of left ventricular performance before and after an intravenous injection of morphine sulphate in two patients with left ventricular failure A.S. and R.T.

Mean Stroke Power Index (Fig. 52) decreased initially in three patients (G.C., A.S., and R.T.), the lowest values (10.1% to 28.2% in different patients) being observed at 1 or 4 minutes after the injection of morphine. Later this measurement returned to control levels at 10, 15 and 25 minutes in R.T., A.S. and G.C. respectively. In only one of these patients (R.T.) an increase in the mean stroke power index was observed after 25 minutes. The fourth patient (T.H.), in whom no significant changes were observed initially, showed a significant decrease in mean stroke power index between 15 and 40 minutes. For the group as a whole a significant decrease of 4.2% and 4.9% in the mean stroke power index was seen during periods 2 and 3, while during period 4 the average values were not significantly different from the control average (Table: 39).

Mean Ejection Flow Index (Fig. 53) showed variable changes but in each patient these were similar to the changes in stroke volume. Thus in two patients (G.C. and T.H.) an initial increase was noted (1 to 10 minutes) while in the other two patients (A.S. and R.T.) a decrease in mean ejection flow index occurred at this time. Later, in patient G.C., the mean ejection flow index remained at a higher average value as compared to the control observations, while in patient A.S. it remained at a lower average value for most of the study period. In another patient (T.H.) it returned to control levels after the initial increase, while in the fourth patient (R.T.) the initial decrease was followed by an increase above the control values. For the group, the overall changes between 10 and 60 minutes showed a small but significant increase of 2.4% and 3.6% during periods 2 and 4 respectively (Table: 39).

Maximum Rate of Pressure Rise in Aorta (Figs. 50 and 51) decreased

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON MEAN STROKE POWER INDEX
IN PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE

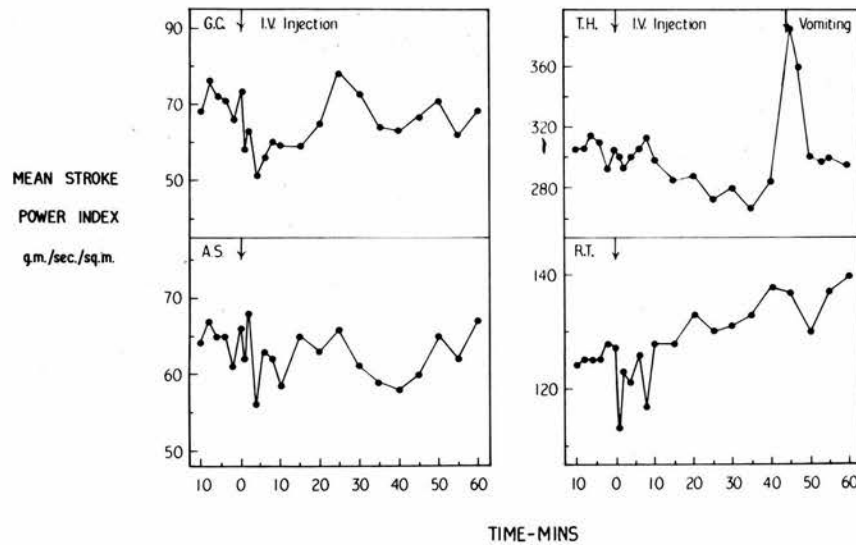


Figure 52

The sequential changes in mean stroke power index before and after an intravenous injection of morphine sulphate in four patients with left ventricular failure.

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON MEAN EJECTION FLOW INDEX
IN PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE

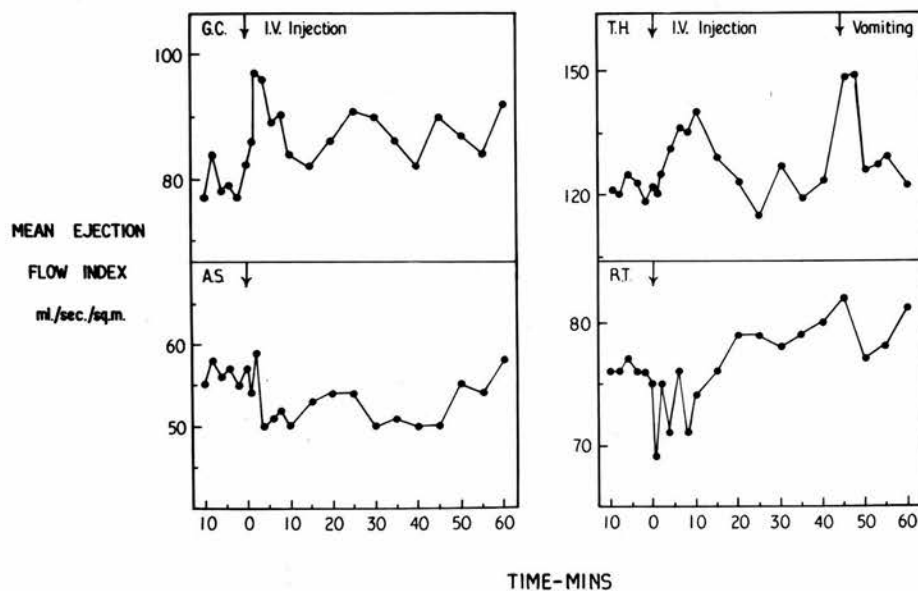


Figure 53

The sequential changes in mean ejection flow index before and after an intravenous injection of morphine sulphate in four patients with left ventricular failure.

in three patients (G.C., T.H. and R.T.) and remained significantly below the range of control observations for most of the study period in all of them. The fourth patient (A.S.) showed an increase between 4 and 30 minutes, the peak of which (33.0%) was observed at 8 minutes. For the group as a whole a highly significant decrease amounting to 5.6%, 9.8% and 7.6% during periods 2, 3 and 4 respectively was observed (Table: 39).

Left Ventricular Minute Work (Figs. 54 and 55) decreased in all four patients after the injection of morphine. In two patients (G.C. and T.H.) it remained below the range of control observations for most of the study period (except period 3 in G.C.). In another patient (A.S.) the left ventricular minute work gradually increased to control levels so that the averages of period 3 and 4 were not significantly different from the control observations. In the fourth patient (R.T.) the left ventricular minute work was within the range of control observations during period 2 but later a small but significant increase was observed. The overall changes during periods 2, 3 and 4 in this group showed a significant decrease amounting to 9.5%, 9.5% and 3.6% respectively (Table: 40).

Mean Aortic Diastolic Pressure (Figs. 54 and 55) decreased in three patients (G.C., T.H. and A.S.) within 2 minutes of the injection of morphine and remained below the level of control observations throughout the study period in two of them (G.C. and T.H.). Because of the large fluctuations in this pressure in the other patient (R.T.), the average changes during periods 2, 3 and 4 were not significantly different from the control average. In the fourth patient (A.S.) the mean aortic diastolic pressure did not show any significant changes up to 40 minutes, after which a small but significant decrease was observed. The overall changes in this group revealed a significant decrease amounting to 6.2%, 5.5% and 7.9% during

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON SOME DETERMINANTS OF CORONARY BLOOD FLOW

IN PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE

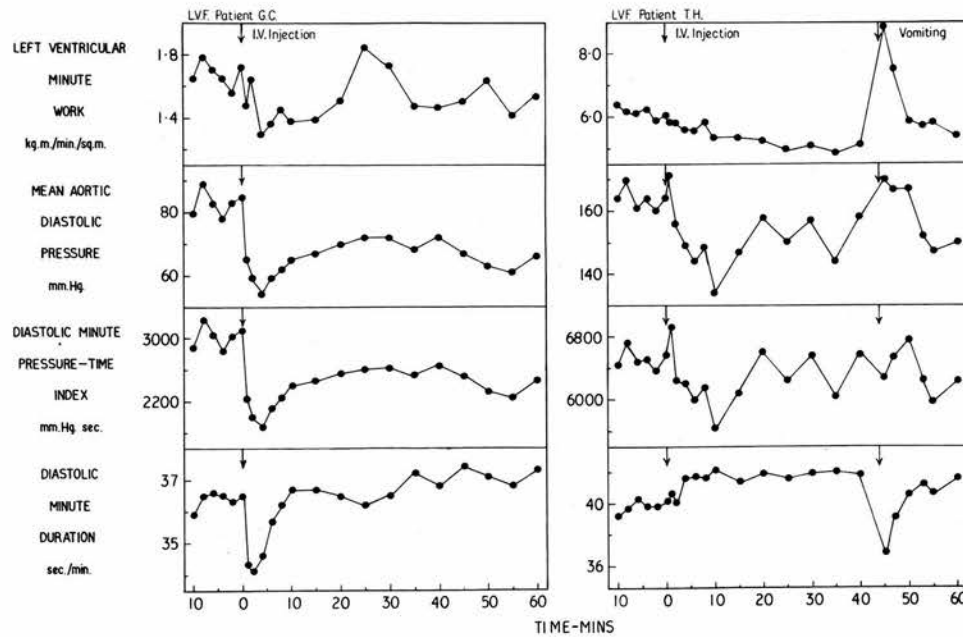


Figure 54

The sequential changes in some determinants of coronary blood flow before and after an intravenous injection of morphine sulphate in two patients with left ventricular failure G.C. and T.H.

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON SOME DETERMINANTS OF CORONARY BLOOD FLOW

IN PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE

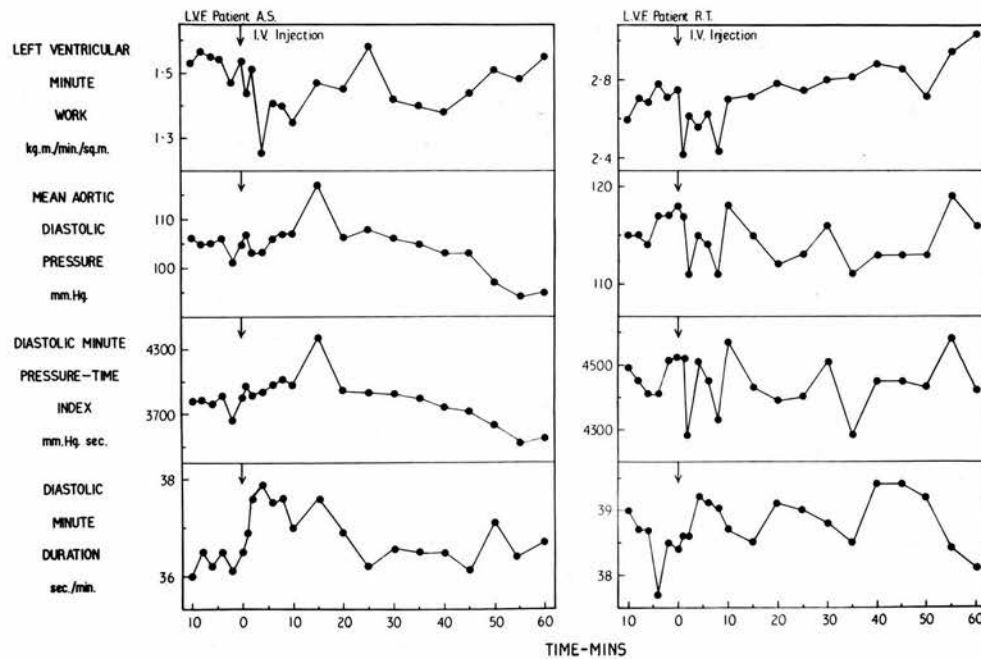


Figure 55

The sequential changes in some determinants of coronary blood flow before and after an intravenous injection of morphine sulphate in two patients with left ventricular failure A.S. and R.T.

periods 2, 3 and 4 respectively (Table: 40).

Duration of Diastole (Table 40) per cardiac cycle varied inversely with the heart rate. However, the diastolic minute duration (Figs. 54 and 55) increased significantly in two patients (T.H. and A.S.) following the injection of morphine. In one of these (T.H.) the increase was maintained throughout the study period, while in the other (A.S.) the diastolic minute duration was within the range of control observations after 25 minutes. One patient (G.C.) showed an initial decrease (between 1 and 8 minutes) and later a small increase (after 35 minutes). The fourth patient (R.T.) did not show any significant changes throughout the study period. In the group as a whole, a significant increase amounting to 2.1%, 1.9% and 1.6% was observed during periods 2, 3 and 4 respectively (Table: 40).

Diastolic Pressure-Time Index (Figs. 54 and 55) showed changes similar to those in the mean aortic diastolic pressure. In one patient (G.C.) a sustained decrease was observed throughout the study period, while in two patients (T.H. and R.T.) large fluctuations were observed after an initial transient decrease, so that the averages of periods 2, 3 and 4 were not significantly different from the control mean. In the fourth patient (A.S.) the only significant change was a decrease of 6.5% during period 4. The overall changes in the group showed a significant decrease amounting to 3.8%, 3.3% and 6.1% during periods 2, 3 and 4 respectively (Table; 40).

Systolic Pressure-Time Index (Fig. 56) decreased immediately after the injection of morphine in two patients (G.C. and T.H.) and remained below control levels for most of the study period. In the other two patients (A.S. and R.T.) no significant changes were observed except for a decrease

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON SYSTOLIC MINUTE PRESSURE-TIME INDEX
IN PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE

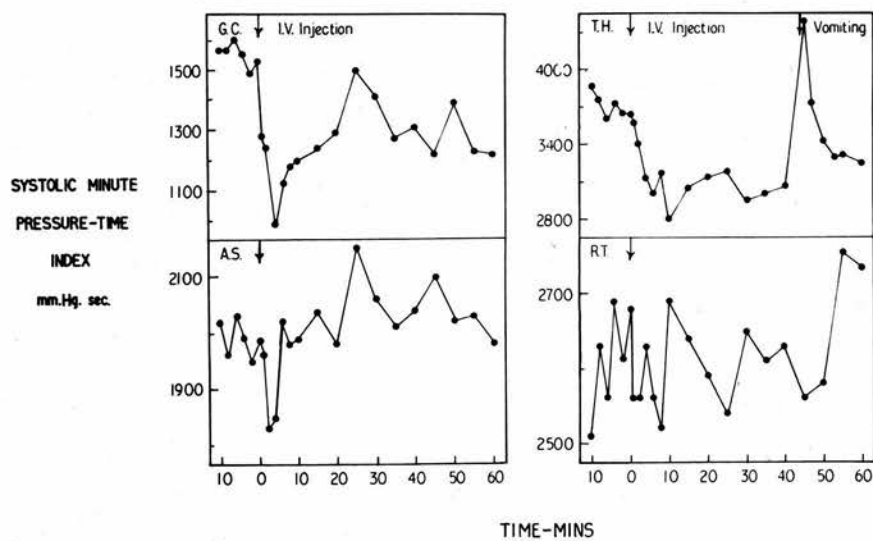


Figure 56

The sequential changes in systolic minute pressure-time index before and after an intravenous injection of morphine sulphate in four patients with left ventricular failure.

during the first 2 minutes in one of them (A.S.). The average values during periods 2, 3 and 4 in this group showed a significant decrease amounting to 9.9%, 7.7% and 5.8% respectively (Table: 40).

The various haemodynamic changes observed during vomiting in patient T.H. have been indicated by an arrow in Figures 43, 45, 46, 47, 49, 50, 52, 53, 54, and 56. Most of the changes reversed within 5 minutes although vascular pressures and heart rate tended to remain elevated longer.

Group III: Mitral Valve Disease Patients

The first dye curve after the injection of morphine in patient L.C. was recorded at 2 minutes. The mean circulation time in this patient was so prolonged that it was not technically feasible to record an additional dye curve at 1 minute.

Cardiac Output (Figs. 57 and 58) increased at one minute by an average of 27.6% (21.7%, 28.5% and 34.0%) in three (W.S., H.J., M.R.) of the four patients, while the oxygen uptake at this time increased significantly (28.7%) in only one of them (H.J.). Later in two of these three patients the cardiac output rapidly decreased to levels significantly below the range of control observations by 8 (H.J.) and 20 (W.S.) minutes. In the third patient (M.R.) the cardiac output also decreased after the initial rise but it stabilised at a level significantly above the range of control observations, and this persisted throughout the study period (Fig. 50). In the fourth patient (L.C.) no significant changes were observed up to 15 minutes, after which the cardiac output decreased

**EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE SYSTEMIC CIRCULATION IN
PATIENTS WITH MITRAL VALVE DISEASE**

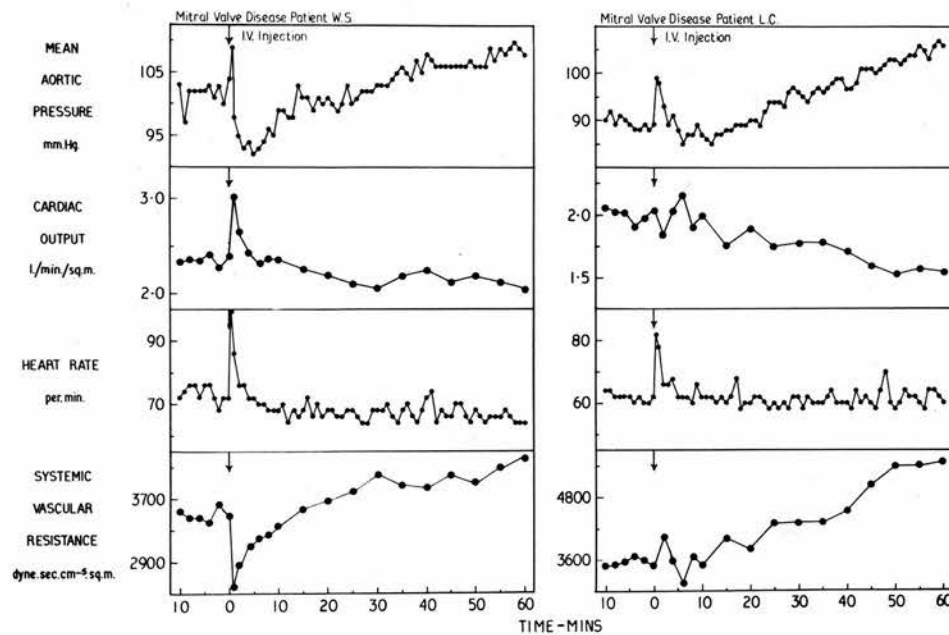


Figure 57

The sequential changes in systemic circulation before and after intravenous injection of morphine sulphate in two patients with mitral valve disease W.S. and L.C.

**EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE SYSTEMIC CIRCULATION IN
PATIENTS WITH MITRAL VALVE DISEASE**

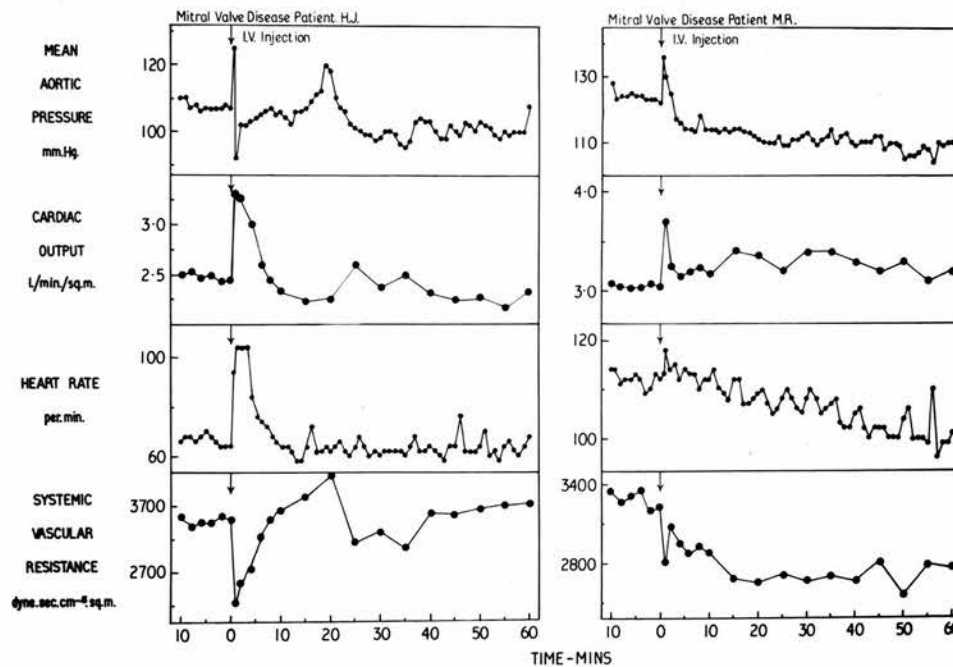


Figure 58

The sequential changes in systemic circulation before and after an intravenous injection of morphine sulphate in two patients with mitral valve disease H.J. and M.R.

below the control levels. The overall changes in the cardiac output between 10 and 60 minutes revealed a significant decrease in this group amounting to 2.0% and 7.7% during periods 3 and 4 respectively (Table:41). When patient M.R. was excluded from the analysis the average decrease during periods 2, 3 and 4 amounted to 6.1%, 7.0% and 13.2% respectively.

Heart Rate (Figs. 57 and 58) increased immediately after the injection of morphine in all four patients, the peak rise, within the first minute, amounting to an average increase of 28.8% (range 5.4% to 56.4%). Subsequently the heart rate rapidly returned to control levels (within 2 to 8 minutes) in all of them, and later even decreased further in three patients (W.S., H.J. and M.R.), while in the fourth patient (L.C.) the heart rate remained within the range of control observations except for a small (2.3%) but significant decrease during period 3 only (Table: 41). For the group the average decreases of 3.7%, 5.4% and 6.6% in the heart rate, during periods 2, 3 and 4 respectively, were found to be highly significant (Table: 41).

Stroke Volume (Fig. 59) showed a differing pattern of response in individual patients. In two patients (W.S. and M.R.) the stroke volume increased by 8.3% and 15.4% at 1 minute, while in the other two patients (L.C. and H.J.) it had decreased by 18.0% and 14.2% at this time. These changes reversed rapidly and later the stroke volume increased again in two patients (H.J. and M.R.) and decreased in the other two (W.S. and L.C.). The average stroke volumes during periods 2 and 3, in this group, were not found to be significantly different from the control mean, but during period 4 the decrease of 4.0% was shown to be statistically significant (Table:41).

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON STROKE VOLUME

IN PATIENTS WITH MITRAL VALVE DISEASE

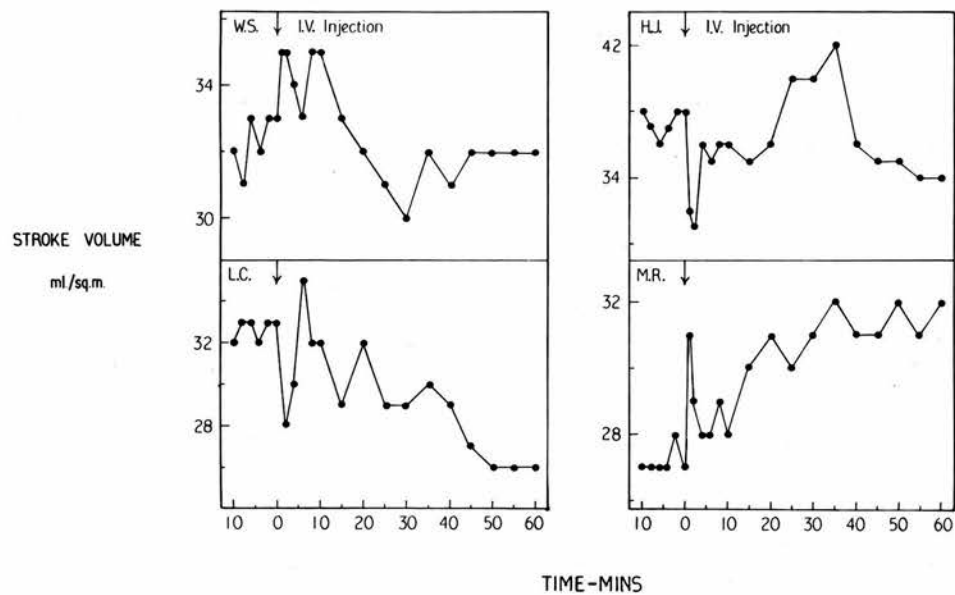


Figure 59

The sequential changes in stroke volume before and after an intravenous injection of morphine sulphate in four patients with mitral valve disease.

Mean Aortic Pressures (Figs. 57 and 58) increased at $\frac{1}{2}$ minute in all four patients by an average of 11.0% (range 7.2% to 16.2%). Subsequently it decreased rapidly, falling below the control levels within 3 minutes in three patients (W.S., H.J. and M.R.). The mean aortic pressure remained below the control levels for most of the study period in two (H.J. and M.R.) of these three patients. In the third patient (W.S.) it gradually increased so that between 10 and 30 minutes this was within the range of control observations, and later even increased above this range. In the fourth patient (L.C.) the initial increase was followed by a short period (3 to 20 minutes) during which the mean aortic pressure remained at control levels, but after 20 minutes it gradually increased throughout the rest of the study period. For the group as a whole, the average changes during periods 2 and 3 were small but significant decreases of 3.0% and 2.9% respectively, but during period 4 the average value was not significantly different from the control average (Table: 41).

Systemic Vascular Resistance (Figs. 57 and 58) decreased in three patients (W.S., H.J. and M.R.) at 1 minute by an average of 25.5% (25.9%, 36.0% and 14.0% respectively). Subsequently this gradually increased in two patients (W.S. and H.J.), stabilising at a level significantly higher than the mean of control observations, while in the third patient (M.R.) the systemic vascular resistance remained significantly below the control mean throughout the study period (Fig. 58). In the fourth patient (L.C.) no significant changes occurred up to 10 minutes, after which the systemic vascular resistance increased progressively. For the group the systemic vascular resistance showed average increases of 1.0%, 2.9% and 14.3% during periods 2, 3 and 4 respectively. These changes were

statistically significant during periods 3 and 4 (Table: 41). If patient M.R., in whom the systemic vascular resistance decreased, be excluded, the average increase during periods 2, 3 and 4 amounted to 6.4%, 9.4% and 23.9% respectively.

Oxygen Uptake (Fig. 60) increased (12.6% and 28.7%) transiently at 1 minute in two patients (L.C. and H.J.) and later decreased in one of them (L.C.), while in the other (H.J.) no consistent changes were observed after the initial increase. Of the remaining two patients, one (M.R.) showed a decrease between 4 and 15 minutes and again between 45 and 60 minutes, while in the other (W.S.) a small increase at 10 minutes was followed by a decrease below the level of control observations. The average changes during periods 2, 3 and 4 in this group, revealed a significant decrease (8.5%) in oxygen uptake during period 4 only (Table:41).

Variable changes were observed initially in the A-V oxygen content difference. In one patient (H.J.) no significant changes were seen initially but later the A-V oxygen content difference widened. Of the remaining three patients the A-V oxygen content difference widened in one (L.C.), while in the other two (W.S. and M.R.), it narrowed initially. Later, however, in two of them an increase in the A-V oxygen content difference was observed while in the third (M.R.) this decreased. The overall average changes during periods 2 and 3 were not significantly different from the control average but during period 4 a significant increase (3.9%) in the A-V oxygen content difference was observed in this group (Table: 41).

Mean Pulmonary Artery Pressure (Figs. 61 and 62) increased in all four patients immediately after the injection of morphine, the peak rise

EFFECT OF A SINGLE INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON OXYGEN UPTAKE IN PATIENTS WITH MITRAL VALVE DISEASE

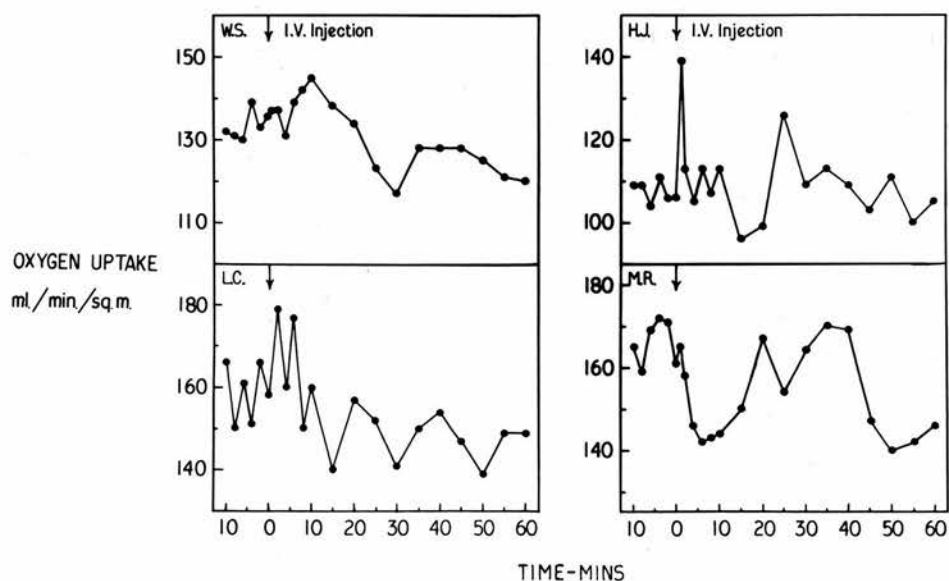


Figure 60

The sequential changes in oxygen uptake before and after an intravenous injection of morphine sulphate on four patients with mitral valve disease.

**EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE PULMONARY CIRCULATION IN
PATIENTS WITH MITRAL VALVE DISEASE**

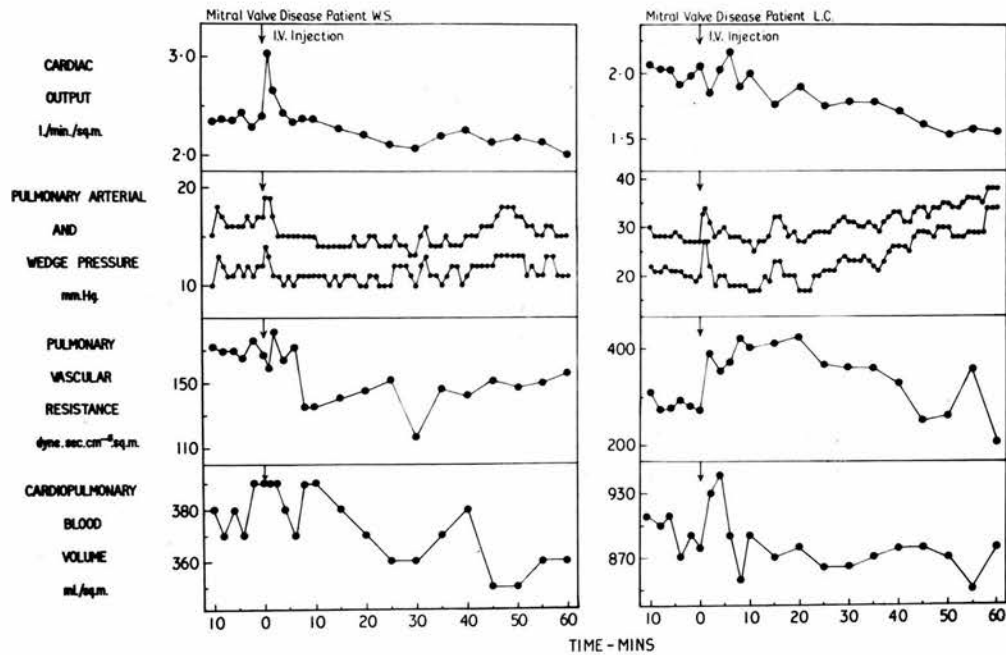


Figure 61

The sequential changes in pulmonary circulation before and after an intravenous injection of morphine sulphate in two patients with mitral valve disease W.S. and L.C.

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON THE PULMONARY CIRCULATION IN
PATIENTS WITH MITRAL VALVE DISEASE

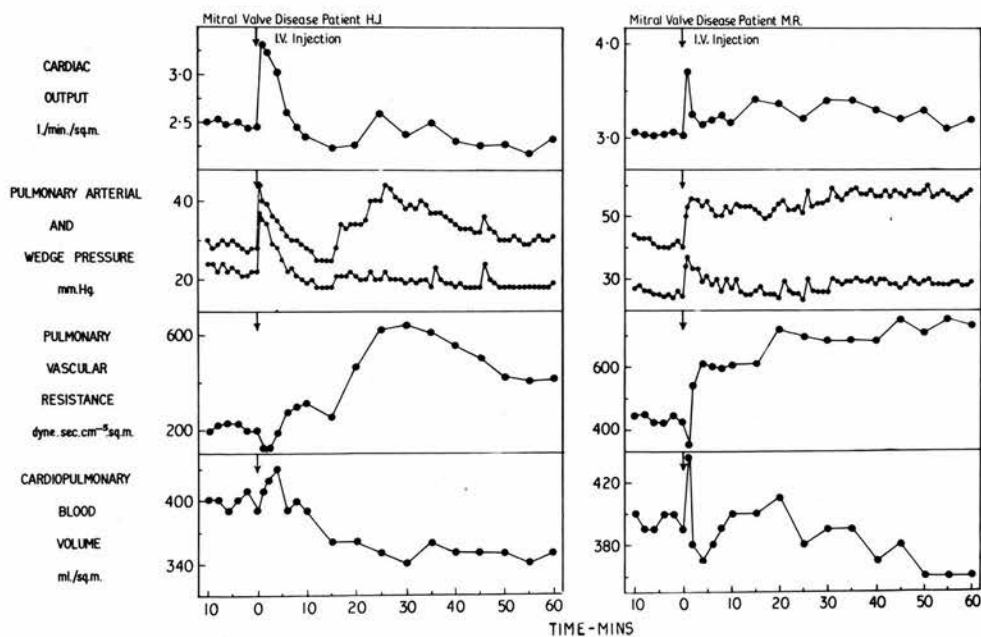


Figure 62

The sequential changes in pulmonary circulation before and after an intravenous injection of morphine sulphate in two patients with mitral valve disease H.J. and M.R.

(15.2% to 53.3%) being observed within 2 minutes. In one patient (M.R.) this increase was maintained throughout the study period, while in two patients (L.C. and H.J.) the mean pulmonary artery pressure decreased to control levels before increasing again (after 28 and 16 minutes respectively). In the fourth patient (W.S.) no initial changes were observed but the mean pulmonary artery pressure was below the range of control observations between 10 and 40 minutes. For the group the average increases of 7.7%, 22.0% and 21.6% in the mean pulmonary artery pressure during periods 2, 3 and 4 were found to be highly significant (Table: 42).

Mean Pulmonary Wedge Pressure (Figs. 61 and 62) increased initially in all four patients. The peak increase (average 43.3%, range 21.7% to 64.4%) was observed within 1 minute of the injection of morphine. Later in all patients the mean pulmonary wedge pressure returned to control levels within 10 minutes, but in two patients (L.C. and M.R.) a further increase was observed after 30 minutes. In one patient only (H.J.) a significant decrease in the mean pulmonary wedge pressure was seen between 8 and 60 minutes, while in the remaining patient (W.S.) it remained within the range of control observations, except for a small (7.8%) but significant decrease during period 2 only. The overall averages of the mean pulmonary wedge pressure during periods 2 and 3 in this group were not significantly different from the control mean but a significant increase of 10.9% was found during period 4 (Table: 42).

Pulmonary Vascular Resistance (Figs. 61 and 62) increased in three patients (L.C., H.J. and M.R.) within 6 minutes although in two of them (H.J. and M.R.) this was preceded by a small decrease at 1 and/or 2 minutes. The rise in pulmonary vascular resistance persisted throughout most of the

study period in all three patients. In the fourth patient (W.S.) the pulmonary vascular resistance decreased at 8 minutes and remained at a level significantly lower than the control figures for the rest of the study period. For the whole group the pulmonary vascular resistance increased significantly by an average of 39.6%, 62.2% and 44.4% during periods 2, 3 and 4 respectively (Table: 42).

Cardiopulmonary Blood Volume (Figs. 61 and 62) increased significantly in three patients (L.C., H.J. and M.R.) initially (1 to 4 minutes) but subsequently decreased in two patients (L.C. and H.J.) while in the third patient (M.R.) a similar decrease was observed after 25 minutes. No significant changes in cardiopulmonary blood volume were seen initially in the fourth patient (W.S.) but after 15 minutes this gradually decreased. For the group as a whole, the average cardiopulmonary blood volume was 1.7%, 4.8% and 6.4% less than the control average during periods 2, 3 and 4 respectively. These changes were found to be statistically significant (Table: 42).

Mean Right Atrial Pressure (Fig. 63) did not show any significant changes in three patients (W.S., L.C. and M.R.) initially, while in one patient (H.J.) it decreased immediately after the injection of morphine and subsequently remained below the level of control observations. A significant increase in the mean right atrial pressure was observed during periods 2, 3 and 4 in one patient (M.R.) and during period 4 in another (W.S.), while in the third patient (L.C.) it decreased during periods 2 and 3. The overall changes in this group were small but statistically significant during periods 2 and 4 (Table: 42).

EFFECTS OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON RIGHT ATRIAL PRESSURE IN

PATIENTS WITH MITRAL VALVE DISEASE

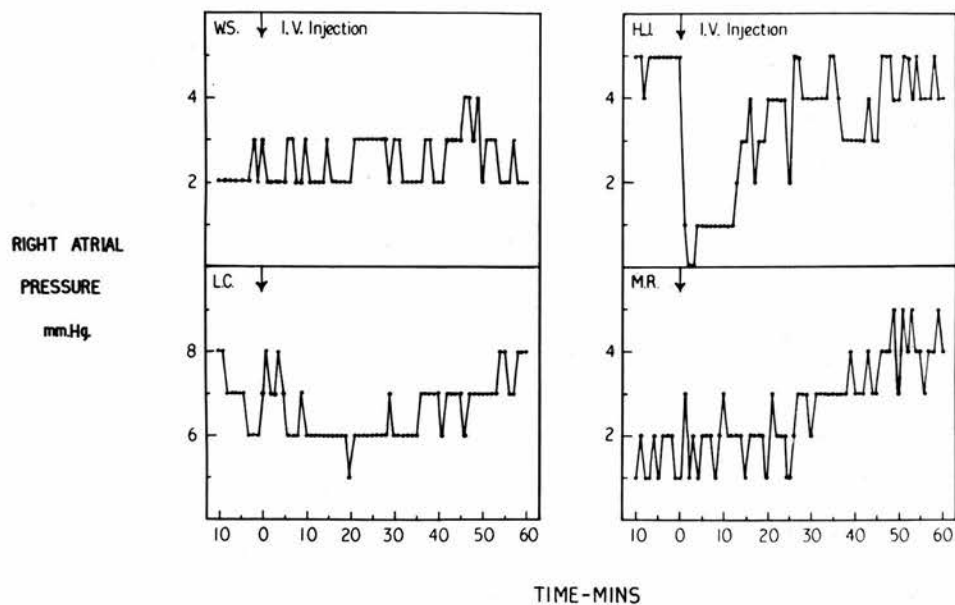


Figure 63

The sequential changes in mean right atrial pressure before and after an intravenous injection of morphine sulphate in four patients with mitral valve disease.

Arterial Blood Gas Tensions and pH (Figs. 64 to 66). The changes in blood gases and pH in individual subjects are presented in Tables 43 to 45. The results of blood gas analyses in two of the six normal subjects were suspect and were thought to be due to a calibration error. These have therefore not been included in the present results. Even so it may be mentioned that the changes in these two subjects were similar to those observed in the rest of them, although the absolute figures were abnormal. The conclusions drawn are not materially affected by discarding this data.

Following the injection of morphine, PO_2 decreased and PCO_2 increased significantly in all subjects of group I (Fig. 64). The arterial pH in these subjects varied inversely with the changes in PCO_2 . These changes were present at five minutes after the injection of morphine (the first post-drug measurement of blood gases was made at this time) in all subjects. Later, in one subject (J.W.), PO_2 was within the range of control observations from 10 minutes onwards while the changes in PCO_2 and pH persisted throughout the study period. In all other subjects the changes in PO_2 as well as PCO_2 and pH persisted throughout the study period. The significance of the difference between the means of the control and post-drug observations for the whole group was assessed by the "Student's" t test and the results are given in Table 46. All three changes, i.e. decrease in PO_2 , increase in PCO_2 and decrease in pH were found to be significant.

Similar changes in PCO_2 and pH were observed in three subjects of Group III (Fig. 65) but the changes in PO_2 were variable (decrease in one and no significant change in two) in these subjects. In the fourth subject (H.J.) a significant increase in PO_2 was observed at five minutes and this was associated with a decrease in PCO_2 and an increase in pH. However, from

THE EFFECT OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE
ON SYSTEMIC ARTERIAL BLOOD GAS TENSIONS AND pH IN NORMAL SUBJECTS

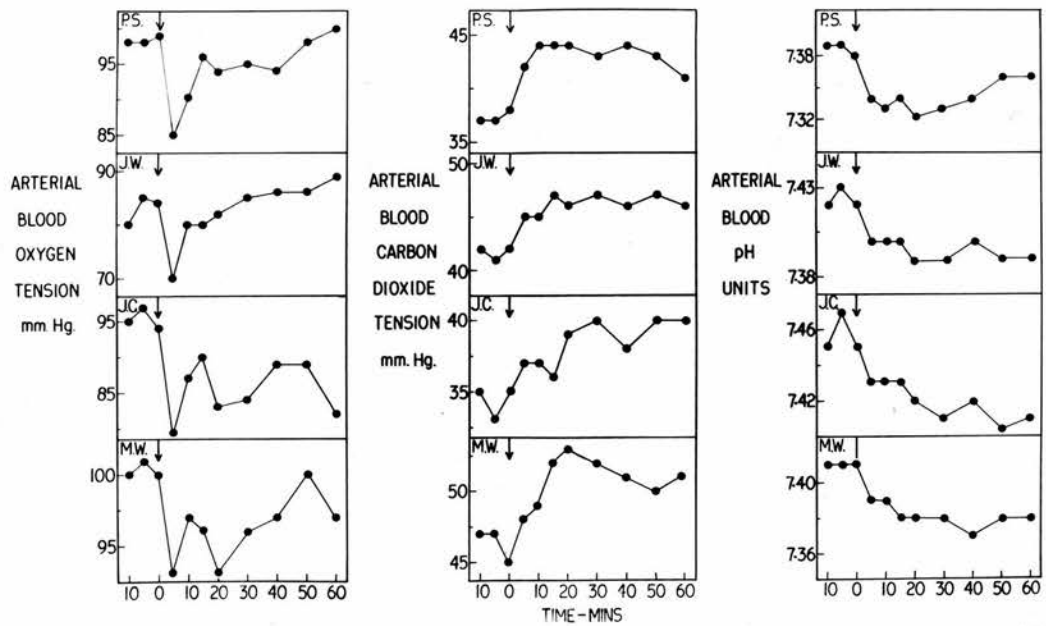


Figure 64

Changes in arterial blood gas tensions and pH before and after intravenous administration of morphine to four normal subjects.

THE EFFECT OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON SYSTEMIC ARTERIAL
BLOOD GAS TENSIONS AND pH IN PATIENTS WITH MITRAL VALVE DISEASE

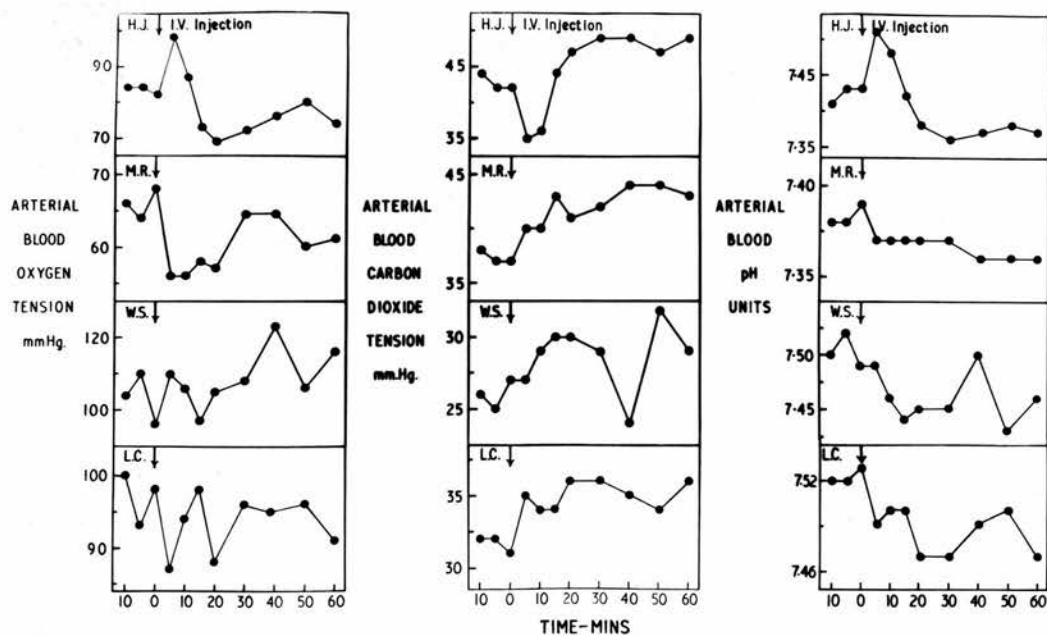


Figure 65

Changes in arterial blood gas tensions and pH before and after intravenous administration of morphine to four patients with mitral valve disease.

THE EFFECT OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON SYSTEMIC ARTERIAL
BLOOD GAS TENSIONS AND pH IN PATIENTS WITH ACUTE LEFT VENTRICULAR FAILURE

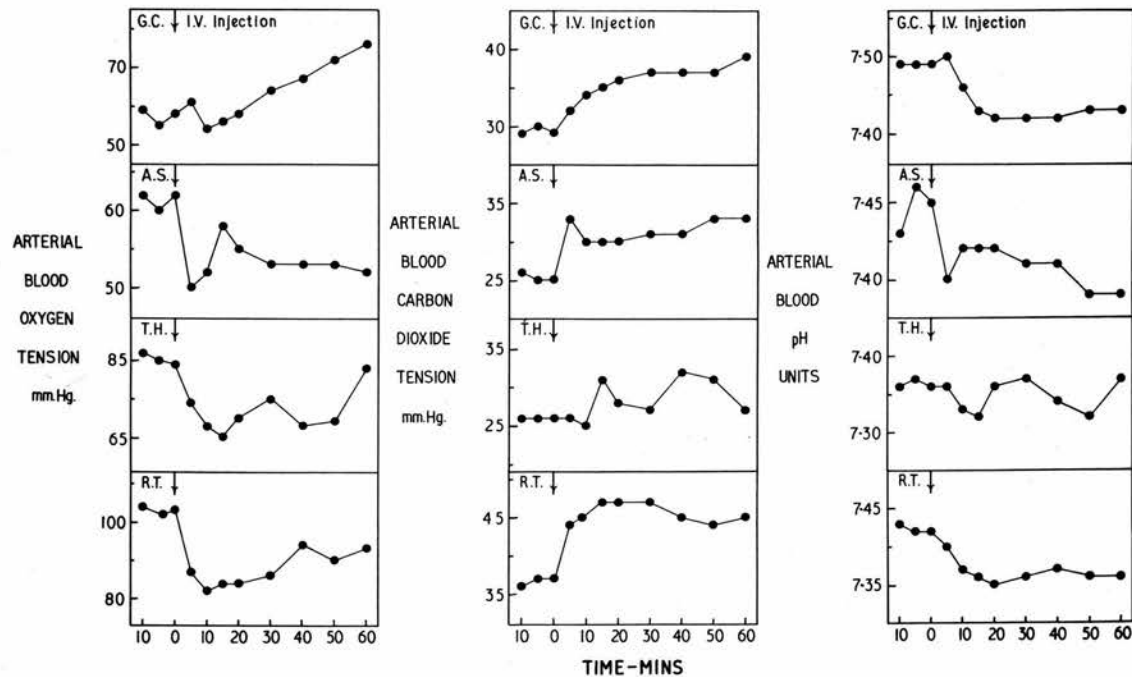


Figure 66

Changes in arterial blood gas tensions and pH before and after intravenous administration of morphine to four patients with left ventricular failure.

THE EFFECT OF AN INTRAVENOUS INJECTION OF MORPHINE SULPHATE ON SYSTEMIC ARTERIAL
BLOOD SUGAR LEVELS

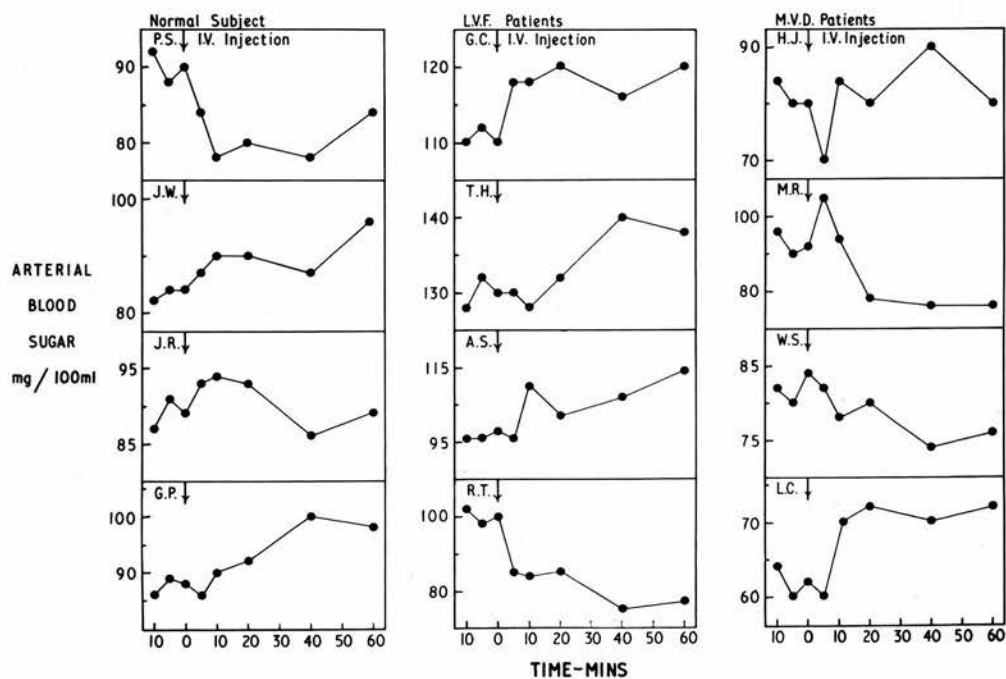


Figure 67

Changes in arterial blood sugar following the intravenous administration of morphine in patients of Groups 1, 2 and 3. For ease of diagrammatic representation, only four patients of group 1 have been plotted but the other two patients also showed similar changes.

10 minutes onwards the changes in this patient were similar to those observed in the other three patients. Statistical treatment of the data was carried out in the same manner as in normal subjects and the results are given in Table 46. The changes in PO_2 for the whole group were not found to be significant while those in PCO_2 and pH were highly significant.

In Group II three of the four patients showed changes in PO_2 , PCO_2 and pH (Fig. 66) which were similar to those observed in normal subjects. In the fourth patient the changes in PCO_2 and pH were also similar but the PO_2 increased progressively from 20 minutes after the injection of morphine. For the group as a whole the changes in PCO_2 and pH were statistically significant while the changes in PO_2 were not significant (Table: 46).

Arterial Blood Sugar (Fig. 67). Variable changes in arterial blood sugar were found in all subjects of groups I, II and III. Detailed data for each subject are given in Table 47 and the results of four subjects in each group are illustrated in Fig. 67. The significance of the difference between the means of the control and post-drug observations in each group was assessed by the "Student's" t test and the results are shown in Table 46. No significant changes were found in any of the three groups.

DISCUSSION

The paucity of adequate published data about the haemodynamic effects of morphine in man makes it difficult to compare the results from the present study with those of other workers. Most of the previous studies include only a few scattered observations in individual subjects and these too were made with relatively insensitive techniques. Only two recent studies in man are available (Thomas et al, 1965; and Roy et al, 1965). Both were

relatively limited in scope and in neither instance were normal subjects included. A brief review of some of the previous reports has been presented in the introduction to this chapter.

The present study demonstrates that morphine, when administered intravenously in therapeutic doses, has a dual action on the cardiovascular system in man. The first of these is exhibited as dramatic but transient haemodynamic changes immediately after the injection following which a second action is manifest in the form of further changes which, though comparatively small in magnitude, are gradual in progression and persist much longer. The two actions are often opposite in direction and may be distinctly separated in time or the second set of changes may follow the first without any such time lag. In the present study an arbitrary temporal division between these two sets of changes has been made to facilitate statistical analysis. The first 10 minutes after the injection of morphine have been taken to represent the "immediate effects" (and their reversal), and these will be discussed first, while later changes are discussed under the category of "delayed effects". It is appreciated that this temporal division is not strictly true in individual subjects and that some degree of overlap is evident from the data. Nevertheless the two sets of effects can be differentiated and their respective significance is discussed in this section.

" IMMEDIATE EFFECTS "(up to 10 minutes)

Groups I and III

Changes in the systemic circulation: Essentially similar changes were observed in both normal subjects (group I) and patients with mitral valve disease (group III). The sudden increase in cardiac output observed in all six normal subjects and three of the four patients with mitral valve disease

was by and large due to an increase in heart rate although the stroke volume also increased in some subjects. This is in accord with the generally accepted view that changes in cardiac output in the supine position are largely rate dependant (Donald et al, 1955; and Bevegård et al, 1960).

Although the maximum increase was observed one minute after the administration of morphine the time course of changes in the heart rate (maximum increase at $\frac{1}{2}$ minute) would suggest that the cardiac output, at one minute, may well have been on the declining limb of these initial changes. However, the aforementioned changes were short lived and reversed within 2 minutes in most and within 3 minutes in all subjects. Failure to observe an increase in cardiac output in one patient (L.C.) of group III could have been due to the fact that the first estimation of cardiac output in this patient was made at 2 minutes by which time the initial changes may well have passed off. This possibility is supported by the increase in heart rate and mean aortic pressure observed at one minute in this patient, which had largely reversed by 2 minutes.

A similar increase in cardiac output within the first 2 minutes after intravenous injection of morphine in man, with or without an increase in heart rate, was also observed in some of their normal subjects by Papper and Bradley (1942) and Drew et al (1946).

The second prominent immediate change was the decrease in systemic vascular resistance observed in all subjects of groups I and III in whom the cardiac output had increased (Figs. 68 and 69). Although this effect was again most marked at one minute and reversed rapidly thereafter, the systemic vascular resistance appears to lag behind the cardiac output in returning to control levels (Figs. 25, 26, 27, 57 and 58). Huggins et al

CHANGES IN CARDIAC OUTPUT, SYSTEMIC VASCULAR RESISTANCE
AND MEAN AORTIC PRESSURE AFTER INTRAVENOUS MORPHINE
IN NORMAL SUBJECTS

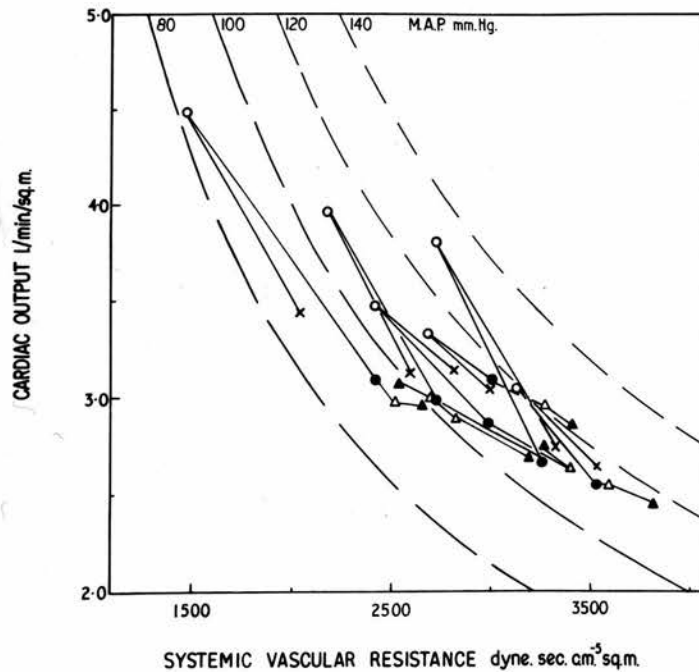


Figure 68

Changes in cardiac output, systemic vascular resistance and mean aortic pressure following intravenous administration of morphine (normal subjects). Crosses represent the average of the control observations and open circles represent the single observation made at 1 minute in each subject. The averages of periods 2, 3 and 4 are represented by solid circles, open triangles and solid triangles respectively. M.A.P. = mean aortic pressure

CHANGES IN CARDIAC OUTPUT, SYSTEMIC VASCULAR RESISTANCE
AND MEAN AORTIC PRESSURE AFTER INTRAVENOUS MORPHINE
IN PATIENTS WITH MITRAL VALVE DISEASE

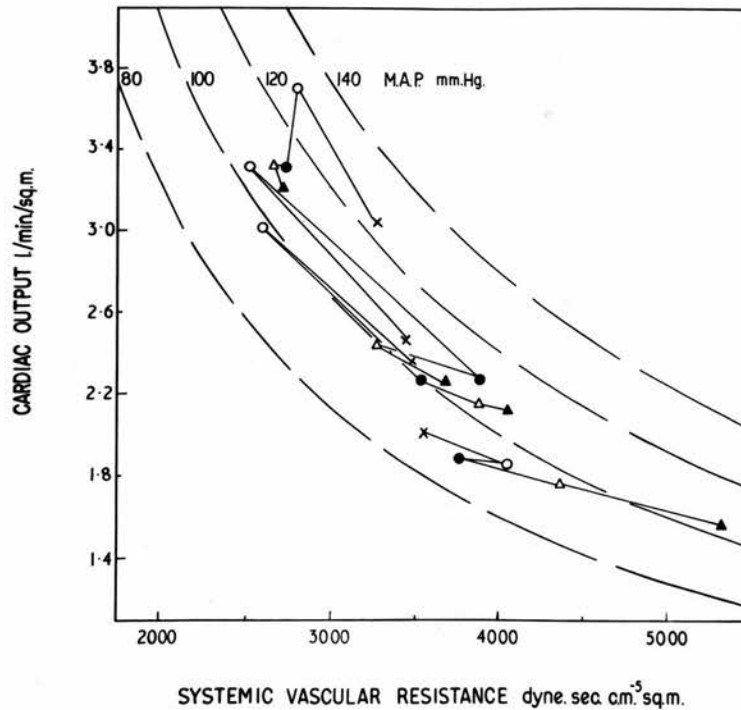


Figure 69

Changes in cardiac output, systemic vascular resistance and mean aortic pressure following intravenous administration of morphine (mitral valve disease patients). Crosses represent the average of the control observations and open circles represent the single observation made at 1 minute in each subject. The averages of periods 2, 3 and 4 are represented by solid circles, open triangles and solid triangles respectively. M.A.P. = mean aortic pressure

(1951) also made a similar observation in their experiments on dogs. Furthermore, a fall in mean aortic pressure, at this time, was seen in four subjects of group I and two patients of group III in spite of the increase in cardiac output. These findings suggest that the initial effect of intravenous morphine is to produce vasodilatation in some or all vascular territories. Several workers have observed a similar decrease in blood pressure, after morphine, in animals, but marked species differences in this response have been reported (Schmidt and Livingstone, 1933; Krueger et al, 1941; Shideman and Johnson, 1948; Huggins et al, 1951; Feldberg and Paton, 1951; Evans et al, 1952; Breckenridge and Hoff, 1952; and Murano and Tanaka, 1957). In human studies on normal supine subjects this initial fall in blood pressure after intravenous morphine has not been a consistent finding (Papper and Bradley, 1942; Drew et al, 1946; and McCall and Taylor, 1952). The orthostatic hypotension observed by several authors is probably unrelated to the phenomenon under discussion and will be referred to later.

The precise mechanism responsible for the vasodilator action of morphine is not known. The subjective sensation of paraesthesia and throbbing headache, also reported by Papper and Bradley (1942) and Dripps and Comroe (1945), together with the skin hyperaemia observed in the present study, indicates that the cutaneous and cerebral vascular territories, at least, participate in this vasodilator response. A transient increase in forearm blood flow and a decrease in forearm vascular resistance immediately after an intravenous injection of morphine (normal subjects; morphine 15 mg/70 kg) has been observed by the author in another study not included in the present report. Huggins et al (1949) have reported an increase in blood flow to the head, following the administration of intravenous morphine in dogs.

The temporal sequence of the paraesthesiae and cutaneous hyperaemia that could be described as "starting in the head and passing out at the toes" is very intriguing and has also been reported after histamine administration (Peters et al., 1945; and Wakim, et al., 1949). The mechanism of this phenomenon is not understood. Although histamine has a direct vasodilator action in man, differences in the circulation time to various parts of the body do not provide a satisfactory explanation. Morphine (and allied drugs) is known to release endogenous histamine in various animal species (Nasmyth and Stewart, 1950; and Feldberg and Paton, 1951). In man, changes in the skin and superficial vessels ^askin to those produced by histamine have been noted by several workers following the administration of morphine (Sollman and Pilcher, 1917; and Nasmyth and Stewart, 1950). However, quantitatively, the concentration of histamine in blood after an intravenous injection of morphine has been found to be less than would be expected for the same degree of vasodilatation (Feldberg and Paton, 1951) and antihistamine compounds do not completely block the vasodilator action of morphine (Feldberg and Paton, 1951; Evans et al., 1952; and Murano and Tanaka, 1957). Furthermore, tolerance to the vasodilator (hypotensive) action of morphine (in common with several other actions) develops rapidly

in several animal species (Schmidt and Livingstone, 1933; and Reynolds and Randall, 1957) but there is no conclusive evidence of such a phenomenon after histamine (Wells et al., 1961). Also animals rendered tolerant to morphine still respond to histamine (Evans et al., 1952). This evidence does not, in itself, exclude the possibility that the hypotensive action of morphine is due to its histamine-liberating properties since tolerance could be due to depletion of the endogenous stores of histamine, although this seems unlikely in view of the large size of the stores, or alternatively these stores may become resistant, in some manner, to the action of morphine.

It has been suggested that tolerance following repeated injections of morphine may be due to its action on the central nervous system and by inference vasodilatation may also be of central origin (Schmidt and Livingstone, 1933; and Shideman and Johnson, 1948). Further, injections of small doses of morphine into the carotid artery of a dog have been shown to produce a transient fall in blood pressure which is usually associated with hyperventilation (Murano and Tanaka, 1957). On the other hand, the hypotensive response is not abolished in

decerebrate animals (Schmidt and Livingstone, 1933) but tolerance no longer develops (Murano and Tanaka, 1957).

The possibility that the hypotensive action of morphine may be mediated through cholinergic nerves is discounted by the failure of both bilateral vagotomy and atropinisation to abolish the response, (Murano and Tanaka, 1957).

Whatever the precise mechanism of the vasodilator action of morphine, it does not seem likely, from the present data, that the increase in cardiac output immediately after the injection of morphine is entirely a secondary response mediated through baroreceptor reflexes. The transient but definite increase in mean aortic pressure, associated with a tachycardia, observed at $\frac{1}{2}$ minute in four of the six subjects of group I and all four subjects of group III suggests that the increase in cardiac output may, in some subjects, lead the vasodilator response by something like 30 seconds. It could, however, be argued that the subjective experiences of these individuals may have contributed to the initial rise in heart rate and cardiac output so that these changes, by themselves, may be somewhat misleading. While this may be true the rapidity with which all the initial changes reverse

(within 2 minutes in most, and within 8 minutes in all) is surprising. Besides, the whole body oxygen uptake did not alter significantly at this time except in two subjects, one each of groups I and III (P.S. and H.J.). The A-V oxygen content difference, as would be expected, narrowed in all subjects.

The significance of the increase in oxygen uptake in these two subjects (P.S. and H.J.) is difficult to evaluate. A transient hyperventilation does occur in some subjects during the first few minutes after injection of morphine and this effect has been shown to be related to the increase in oxygen uptake at this time. This hyperventilation is thought to be a "true drug effect" since it has been shown to be inversely related to the administered dose (Habib, 1966). In this connection it is of interest to note that infusion of histamine has also been shown to produce hyperventilation (Peters et al, 1945; and Lindell et al, 1964), the magnitude of which is dose related. Further evidence suggesting transient hyperventilation after intravenous morphine is found in the reports of Dripps and Comroe (1945) and Johnson (1951). Since ventilation was not measured no comments on the possible relationship between hyperventilation and the increase in oxygen uptake can be made on the basis of the present study.

If the initial increase in mean aortic pressure and heart rate be accepted as a "true drug effect" the inference would then be that the increase in cardiac output and the peripheral vasodilatation are produced by two independent mechanisms. While both may be of central origin the evidence cited above is far from conclusive. It has been claimed from experiments on isolated hearts that morphine has an initial stimulatory action on the mammalian heart followed by depression of both frequency and

amplitude of contraction (Gruber and Robinson, 1929; Schmidt and Livingstone, 1933; and Krueger et al, 1941).

Since histamine release has been implicated in the vasodilator action of morphine it would be pertinent to enquire if this could be responsible for the initial cardioacceleration and increase in cardiac output. Most studies on the effects of histamine (infusion) in man report an increase in heart rate and cardiac output which is considered to be secondary to its vasodilator action (Sterstein et al, 1959; and Westling, 1963). On the other hand, changes similar to those observed in the present study, i.e. an initial tachycardia with or without increase in blood pressure within 15 to 25 seconds, have been reported after a single intravenous injection of histamine (Weiss et al, 1932). It is generally stated that histamine does not have a direct action on the myocardium (Duner and Pernow, 1960), but studies on isolated guinea pig, rat and rabbit atria (Penna et al, 1959; and Trendelenburg, 1960) have revealed a direct stimulant action of histamine (on frequency and amplitude of contraction) which is not blocked by antihistamine compounds (Trendelenburg, 1960).

In the absence of conclusive evidence either way the possibility that morphine may have a transient stimulant action (initially) on the heart in man, the mechanism of which is purely speculative at present, must be considered in future investigations. It may be mentioned in passing that morphine is known to have a stimulatory action when administered in sufficiently large doses to some animal species, in particular cats; and in man excitatory phenomena have also been reported occasionally. Further, morphine has also been shown to have qualitatively different actions (stimulatory or depressant) at different levels of the central nervous

system (Krueger et al, 1941; Wikler, 1950; and Reynolds and Randall, 1957). The relevance of these known actions of morphine to the initial stimulatory action on the heart observed in the present study is conjectural. Further work on these lines may yield more definite information.

Changes in the Pulmonary Circulation: The immediate changes in the pulmonary circulation following intravenous morphine were somewhat different in patients with mitral valve disease (group III) as compared to the normal subjects (group I). While a significant but transient increase in mean pulmonary artery and wedge pressures was seen in all subjects of group III, a similar change occurred in only two of the six subjects of group I. On the other hand, the pulmonary vascular resistance increased in three subjects of group I within the first 4 minutes, at a time when the cardiac output was back at normal levels or still elevated, while in two of the four subjects of group III it decreased with the increase in pulmonary blood flow. In the absence of knowledge about changes in ventilation and intrathoracic pressures the functional significance of these changes is difficult to evaluate. For the most part, however, they would appear to be passive in nature.

There are no comparable studies in the literature in which immediate changes in pulmonary circulation after intravenous morphine have been reported. Of the various mechanisms that may be responsible for the initial systemic circulatory changes produced by morphine (vide supra) information about their effects on pulmonary circulation is available only with respect to histamine. Variable changes in the pulmonary circulation have been reported after intravenous histamine in man (Aviado, 1960; Westling, 1963) and other animals (Woodbury and Hamilton, 1941) but a decrease in pulmonary vascular resistance has been observed more frequently in patients with mitral

valve disease than in normal subjects (Westling, 1963; and Lindell et al, 1964).

The cardiopulmonary blood volume either increased (group I: two subjects and group III: three subjects) or did not alter (group I: three subjects and group III: one subject) while the cardiac output was elevated, but it decreased significantly in most subjects soon after the latter had returned to control levels. The mean right atrial pressure decreased in five subjects (group I: four subjects and group III: one subject) at this time but these changes were not consistently related to the changes in cardiopulmonary blood volume.

Changes in Left Ventricular Performance: For reasons previously mentioned indices of left ventricular performance were measured in normal subjects but not in patients with mitral valve disease.

One minute after the injection of morphine the left ventricular stroke work increased but the mean pulmonary wedge pressure did not alter significantly in two subjects (P.S. and G.P.) of group I, while in another subject (J.R.) mean pulmonary wedge pressure decreased without any significant change in stroke work. Of the remaining three subjects, two did not show any significant changes in either parameter while both stroke work and mean pulmonary wedge pressure increased in the third subject (Fig. 70). On the other hand, an increase in mean stroke power index (Fig. 71) and mean ejection flow index (Fig. 38) was observed in all subjects during the first minute.

It has been, recently, demonstrated that an increase in heart rate alone (in normal and abnormal but compensated hearts) produced by atrial or ventricular pacing, results in a decrease in stroke work, mean stroke power

CHANGES IN STROKE WORK AND MEAN PULMONARY WEDGE PRESSURE
AFTER INTRAVENOUS MORPHINE SULPHATE IN NORMAL PATIENTS

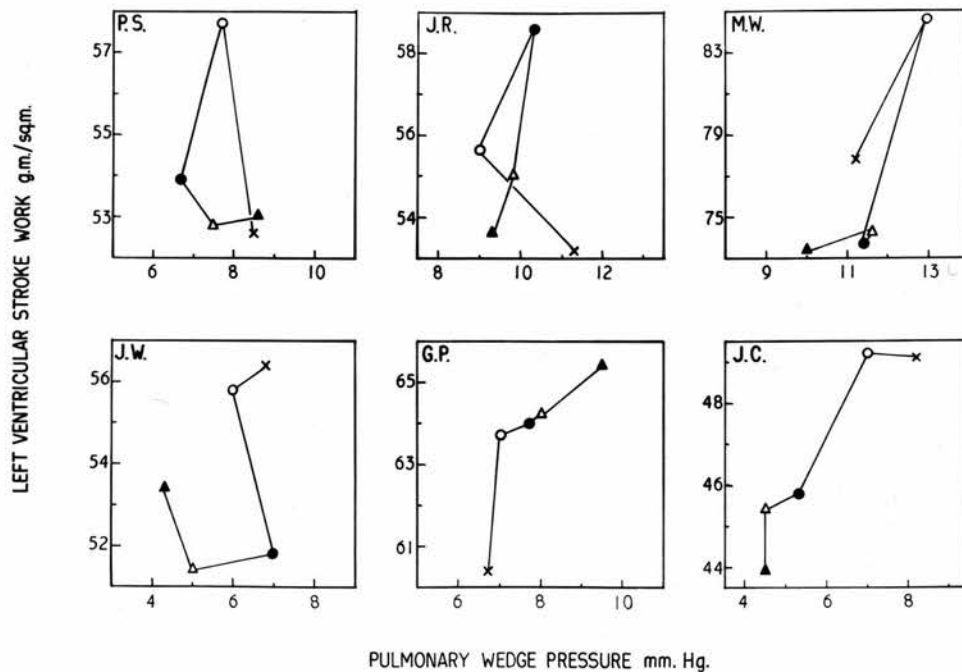


Figure 70

Changes in left ventricular stroke work and mean pulmonary wedge pressure in six normal subjects following the intravenous administration of morphine. Crosses represent the average of control observations, open circles represent the single observation at 1 minute, and the average values of periods 2, 3 and 4 are represented by solid circles, open triangles and solid triangles respectively.

CHANGES IN STROKE POWER AND MEAN PULMONARY WEDGE PRESSURE
AFTER INTRAVENOUS MORPHINE SULPHATE IN NORMAL PATIENTS

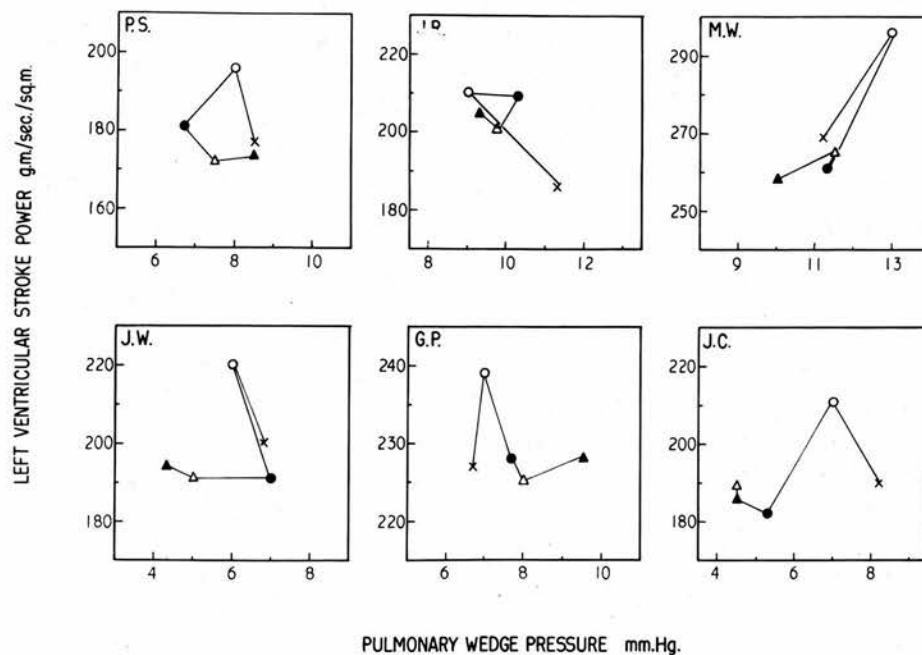


Figure 71

Changes in left ventricular stroke power and mean pulmonary wedge pressure in six normal subjects following the intravenous administration of morphine. Crosses represent the average of control observations, open circles represent the single observation at 1 minute, and the average values of periods 2, 3 and 4 are represented by solid circles, open triangles and solid triangles respectively.

and mean ejection flow, while minute work and cardiac output do not alter (Stein et al, 1966; and Benchimol and Liggett, 1966). It has also been shown that the peak contractile force of the right ventricle does not alter significantly with changes in heart rate (Sonnenblick et al, 1966) thus providing evidence that the "Bowditch effect" is not demonstrable in the intact human heart. On the strength of this evidence the findings from the present study indicate that myocardial contractility is increased, independent of the tachycardia, immediately after the injection of morphine. The change is, however, transient and reverses rapidly. This would be in accord with the initial stimulatory effect of morphine found in animal experiments on isolated hearts and already referred to.

The left ventricular minute work increased transiently at one minute in all six subjects of group I. This was mainly due to the increase in cardiac output while mean systolic ejection pressure either did not alter or even decreased. Variable changes were seen in the systolic minute pressure-time index in these subjects (increase in three, decrease in two, and no significant change in one). Since the oxygen cost of increased "flow work" is much less than that of increased "pressure work" (Katz, 1955; and Sarnoff et al, 1958) myocardial oxygen consumption presumably did not alter significantly. The initial decrease in diastolic minute pressure-time index, due both to a decrease in mean aortic diastolic pressure and diastolic minute duration, would imply a decrease in coronary blood flow provided coronary vascular resistance did not alter. However, from the present study, no direct information about the latter is available. In animals, morphine has been shown to lead to increased coronary blood flow (Krueger et al, 1941; and Reynolds and Randall, 1957).

Group II

Changes in the Systemic Circulation: Immediate changes in the four patients in left ventricular failure (group II) were different from those observed in normal subjects or patients with mitral valve disease. The initial increase in heart rate and cardiac output, seen in nine of the ten subjects of groups I and III, was observed in only one patient (G.C.) with left ventricular failure. The cardiac output decreased in another two patients while no significant change was seen in the fourth patient. The whole body oxygen uptake increased transiently in two of the four patients. Both patients in whom the cardiac output decreased were able to maintain their mean aortic pressure at control levels (one showed a small increase) due to the increase in systemic vascular resistance. On the other hand, both the systemic vascular resistance and mean aortic pressure decreased in the other two patients in whom cardiac output either increased or did not change (Fig. 72). This variation in response indicates that the vasodilator action of morphine is, in some instances, modified by the pre-existing haemodynamic background.

Increased urinary concentration of catecholamines (noradrenaline) has been demonstrated in heart failure and shown to be inversely related to the catecholamine content of the myocardium (Chidsey et al, 1965) which in turn is directly related to the tension developed by the muscle (Chidsey et al, 1966). Implied in these findings is that the functional state of the failing myocardium is inversely related to the level of circulating catecholamines and this accords well with the clinical observations in this condition. It is possible, therefore, that the initial vasodilator response to morphine may be prevented by the marked vasoconstrictor action of circulating noradrenaline in some patients in heart failure. Although generalisations are

CHANGES IN CARDIAC OUTPUT, SYSTEMIC VASCULAR RESISTANCE
AND MEAN AORTIC PRESSURE AFTER INTRAVENOUS MORPHINE
IN PATIENTS WITH LEFT VENTRICULAR FAILURE

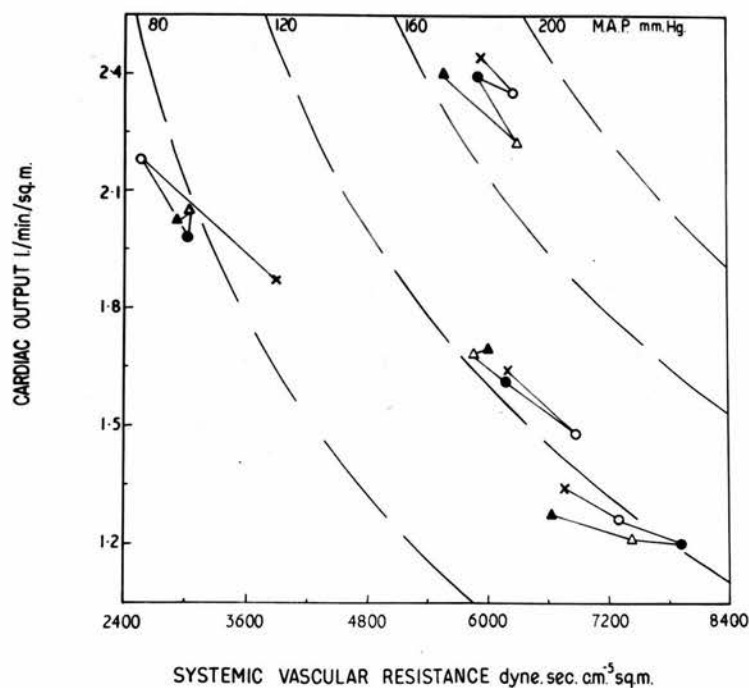


Figure 72

Changes in cardiac output, systemic vascular resistance and mean aortic pressure following intravenous administration of morphine (patients with left ventricular failure). Crosses represent the average of the control observations and open circles represent the single observation made at 1 minute in each subject. The average of periods 2, 3 and 4 are represented by solid circles, open triangles and solid triangles respectively. M.A.P. = mean aortic pressure.

not possible. from this small sample, it is worthy of note that the resting cardiac outputs in the two patients who did not show a fall in systemic vascular resistance were lower (1.34 and 1.64 l./min./sq.m.) as compared to the other two patients (1.87 and 2.44 l./min./sq.m.) and it may well be that the functional state of the myocardium was depressed to different degrees in individual patients. However, the precise mechanisms that could account for the differences in the initial response to morphine in compensated and decompensated states cannot be deduced from the present study.

Changes in the Pulmonary Circulation: Changes in the pulmonary circulation were variable though more marked in patients with left ventricular failure as compared to the other two groups. In two patients both the mean pulmonary artery and wedge pressures decreased while in the other two patients an increase was observed during the first few minutes after morphine. Variable changes (increase in two and decrease in two) were also seen in the pulmonary vascular resistance. The difficulties in the interpretation of these changes have been already pointed out.

The cardiopulmonary blood volume increased transiently in two patients at first but soon decreased below the control levels in all four patients. The latter findings will be discussed further when dealing with "delayed effects".

The mean right atrial pressure decreased in two, increased in one and did not change in another patient. These changes did not bear any consistent relation to the changes in cardiopulmonary blood volume.

Changes in Left Ventricular Performance: The decrease in stroke work and mean stroke power index at one minute (in four and three patients respectively) in these patients was associated with a decrease in mean

pulmonary wedge pressure in only one patient (Figs. 73 and 74). The mean ejection flow index at this time increased in two patients and decreased in the other two.

It is difficult to assess the possible changes in left ventricular function from this data but there is no evidence of an improvement in myocardial contractility, in patients with left ventricular failure immediately after the injection of morphine. Whether the converse is true cannot be judged for certain from the present data. This apparent difference from the results obtained in normal subjects is easily reconciled by the fact that the left ventricle, in a state of decompensation, is operating on a relatively flat length-tension curve, so that the comparatively weak stimulant action of morphine is unlikely to produce a demonstrable effect on its contractile function. Furthermore, the failing ventricle is probably already under marked neuro-humoral stimulation (vide supra).

Left ventricular minute work decreased in three of the four patients and the systolic minute pressure-time index decreased in all four patients (significant in three). Both changes were mainly due to the decrease in mean systolic ejection pressure. The functional significance of this presumed reduction in myocardial oxygen consumption is not apparent from the present study. The diastolic minute-pressure-time index also decreased in three patients.

"DELAYED EFFECTS" (10 - 60 minutes)

Following the immediate but transient response already discussed further haemodynamic changes were observed in all three groups of subjects. In some subjects these commenced 10 to 25 minutes after the injection of morphine being separated from the initial changes by a brief period during which most variables were at their respective control levels. In other

CHANGES IN STROKE WORK AND MEAN PULMONARY WEDGE PRESSURE
AFTER INTRAVENOUS MORPHINE SULPHATE IN PATIENTS
WITH LEFT VENTRICULAR FAILURE

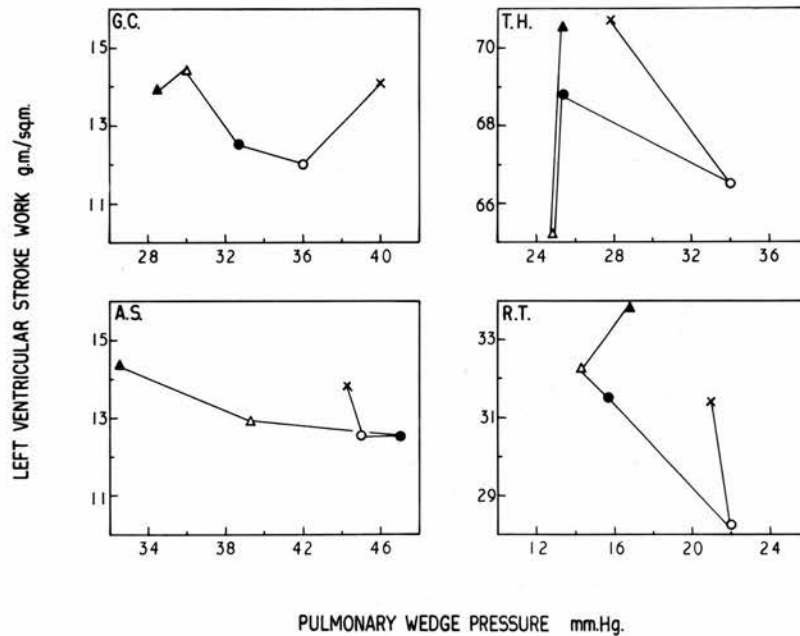


Figure 73

Changes in left ventricular stroke work and mean pulmonary wedge pressure in four patients with left ventricular failure following the intravenous administration of morphine. Crosses represent the average of control observations, open circles represent the single observation at 1 minute, and the average values of periods 2, 3 and 4 are represented by solid circles, open triangles and solid triangles respectively.

CHANGES IN STROKE POWER AND MEAN PULMONARY WEDGE PRESSURE
AFTER INTRAVENOUS MORPHINE SULPHATE IN PATIENTS
WITH LEFT VENTRICULAR FAILURE

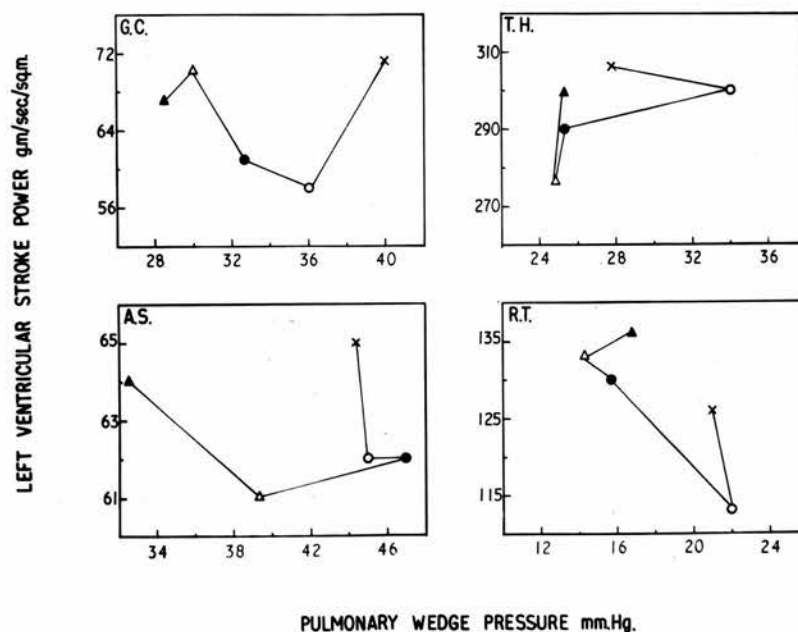


Figure 74

Changes in left ventricular stroke power and mean pulmonary wedge pressure in four patients with left ventricular failure following the intravenous administration of morphine. Crosses represent the average of control observations, open circles represent the single observation at 1 minute, and the average values of periods 2, 3 and 4 are represented by solid circles, open triangles and solid triangles respectively.

subjects no such intervening period could be made out, the "delayed effects" merging imperceptibly with the declining limb of the "immediate effects". While these late changes were much less dramatic in magnitude they were generally sustained much longer and (as will be apparent from the ensuing discussion) would appear to be of therapeutic importance.

Groups I and III

Changes in the Systemic Circulation: Both normal subjects (group I) and patients with mitral valve disease (group III) showed an essentially similar response. Except for one subject in each of these two groups, the cardiac output decreased significantly (group I: five subjects and group III: three subjects) within 20 to 25 minutes and remained below the control levels throughout the rest of the study period. This reduction in cardiac output was of the order of 3.4% to 22.4% in individual subjects and was due to a decrease in heart rate and/or stroke volume, the former being a more consistent finding than the latter.

The whole body oxygen uptake also showed a general trend towards a decrease during this time, although in some subjects (particularly group III) individual changes were not statistically significant. The A-V oxygen content difference widened significantly in four (group I: three subjects and group III: one subject) of these eight subjects, indicating that the decrease in cardiac output was more marked than the reduction in whole body oxygen uptake. The significance of this difference is difficult to assess since whole body oxygen uptake was not directly measured in the present study and the errors in estimating oxygen saturation in mixed venous blood (at low levels of SO_2), by the method used, can be relatively large (Chapter II). A decrease in whole body oxygen uptake in man following intravenous morphine in doses greater than 10mg/70 kg. has also been reported

recently (Habib, 1966). Since the reduction in oxygen uptake was not found to be correlated with the decrease in ventilation it has been postulated that the results are indicative of an increase in metabolism. An increase in carbon dioxide output, observed by the same author, was considered to be corroborative evidence for his hypothesis (Habib, 1966). Earlier workers have found variable changes in oxygen uptake, i.e. decrease, no change, or even an increase following the administration of morphine (Starr et al, 1937; Wangeman and Hawk, 1942; Johnson, 1951; Keats and Beecher, 1952; and Orkin et al, 1955). Large doses of morphine usually produce a fall in body temperature but the effect of small doses is variable and slight, if any (Reynolds and Randall, 1957). Similarly, hyperglycaemia (thought to be due to the stimulation of supraspinal autonomic centres leading to the release of adrenaline from the adrenal medulla) has not been consistently observed in man although it is more commonly seen in some animal species (for references see Krueger et al, 1941; Reynolds and Randall, 1957; and Goodman and Gillman, 1965). Changes in blood sugar in the present study were variable. While individual subjects showed an increase or decrease, the mean changes in each of the three groups were not statistically significant. It is difficult to reconcile the differences between various studies, and the precise effect of morphine on body metabolism in man remains an open question.

In both groups I and III the mean aortic pressure remained, for the most part, within the range of control observations or even increased in the eight subjects in whom the cardiac output decreased. The systemic vascular resistance consistently increased (5.5% to 49.9%) above the control levels in these eight subjects (Figs. 68 and 69). Whether these changes are purely compensatory in nature or involve functional changes in various

cardiovascular reflexes cannot be determined from the present study.

It is worthy of note that a small but significant increase in mean aortic pressure above the control levels, was observed in five subjects (three in group I and two in group III) in spite of the fall in cardiac output. It has been claimed that baroreceptor reflexes and /or the vasomotor centre are depressed by morphine but there is no consensus of opinion about such effects of morphine (Krueger et al, 1941; and Eckenhoff and Oech, 1960).

Changes in the systemic circulation in two subjects (J.W. and M.R.)

- one each of groups I and III - are of further interest. In both subjects (Figs. 25 and 58) the mean aortic pressure decreased progressively (by 16.8% and 18.0% at its lowest) after the initial changes (decrease in one and increase in another) in this parameter had reversed. This was due to a secondary decrease in the systemic vascular resistance which persisted throughout the study period in contrast to the transient initial decrease. Associated with these changes was a secondary rise in cardiac output which also persisted throughout the study period. The magnitude of this increase in cardiac output was, however, less than that of the initial increase.

The mechanism of these changes is conjectural. The present study shows that this "delayed" hypotensive effect is not a consistent action of morphine, as is also evident from the data of Drew et al (1946) and Thomas et al (1965) and many other published observations of hypotension after this and other narcotics. It would appear that some subjects are sensitive to the vasodilator action of morphine and the compensatory mechanisms in these cases are inadequate so that the blood pressure falls. This may well comprise a form of idiosyncrasy to the drug. The marked hypotension following intravenous morphine observed by Thomas et al (1965) in one of their 13 patients with acute myocardial infarction would appear to be on a

similar basis (vide infra). The author would like to emphasise the difference between the "immediate" and "delayed" hypotensive actions of morphine which, as far as can be ascertained, have been described for the first time in man, although reference to a similar phenomenon in animals can be occasionally found (Shideman and Johnson, 1948; and Reynolds and Randall, 1957). Whether the mechanisms of these two changes are different or not is not known at present, but the distinct temporal separation between the two would lend weight to the former possibility.

In both groups I and III a small but significant decrease in heart rate was more frequently (seven subjects) observed than an increase (three subjects). Although bradycardia has been a frequent effect of morphine in animals, particularly dogs, this is by no means invariable (Krueger et al, 1941; Drew et al, 1946; and Eckenhoff and Oech, 1960). Stimulation of the vagal nucleus has been suggested as the mechanism of bradycardia after morphine but evidence in this regard is not conclusive (Wikler, 1950). In the present study marked sinus bradycardia (19.7%) was observed in only one subject (G.P.) in group I. Another subject in this group (J.R.) developed a marked sinus arrhythmia. Irregularities of rhythm and conduction defects have been noted in both man and animals but the mechanism of these changes is not known (Reynolds and Randall, 1957).

Changes in the Pulmonary Circulation: The increase in mean pulmonary artery pressure observed in patients with mitral valve disease was not seen in normal subjects. On the other hand mean pulmonary wedge pressure decreased significantly in these subjects (one exception) while it increased in two of the four patients with mitral valve disease. Except for two subjects (one in each group) the pulmonary vascular resistance increased in both groups.

No information is available from other sources about the effects of morphine on pulmonary circulation in normal subjects. Because of the complex factors that affect pulmonary vascular resistance (Fishman, 1963) it is not possible to arrive at a firm conclusion with regard to the changes in pulmonary vasometricity produced by morphine. Alveolar hypoventilation per se results in an increase in pulmonary vascular resistance, the mechanism of which is not definitely known but hypoxia is probably partly responsible. Similarly a decrease in pulmonary blood flow also leads to an increase in pulmonary vascular resistance (Fishman, 1963).

Evidence of hypoventilation in subjects of group I is provided by the observed changes in blood gases (Fig. 64). A significant decrease in PO_2 associated with an increase in PCO_2 and a fall in pH was found in this group. Similar changes in PCO_2 and pH were also observed in patients of group III but the changes in PO_2 in these patients were variable (Fig. 65). In fact the reduction in ventilation produced by morphine is one of its best documented effects (Krueger et al, 1941; Reynolds and Randall, 1957; Eckenhooff and Oech, 1960; and Habib, 1966).

Although pulmonary blood flow decreased in a majority of subjects this alone cannot be invoked as the only possible mechanism leading to increased pulmonary vascular resistance since the latter was observed even in patients in whom the pulmonary blood flow increased.

The increase in mean pulmonary artery pressure in patients with mitral valve disease could have been due to the abnormal reaction of the pathological pulmonary vascular tree in this disorder. Fejfar et al (1957) also reported a similar increase in mean pulmonary artery pressure in patients with mitral stenosis given intravenous morphine, and the magnitude of this increase was found to be directly related to the level of the control pressure. A

similar pattern was seen in the present study. Only the patient with the lowest mean pulmonary artery pressure in this group (W.S.) did not show an increase, while the maximum increase was seen in the patient with the highest control pressure (M.R.).

The small but significant decrease in mean pulmonary wedge pressure in group I is, in the author's opinion, an important finding and will be discussed further later. A similar finding was seen in only one subject of group III, while the mean pulmonary wedge pressure increased in another two subjects. The latter finding is difficult to explain. The increase in pulmonary blood flow in one of these two subjects may well have been contributory, but the opposite change in pulmonary blood flow was observed in the other subject. In both instances the cardiopulmonary blood volume decreased.

The cardiopulmonary blood volume decreased in four of the six subjects of group I and all four patients of group III, suggesting a shift of blood from the "central reservoir" to the periphery. The variable changes in mean right atrial pressure are not surprising in view of the highly compliant nature of this chamber and the adjoining great veins. A similar decrease in pulmonary blood volume has been reported in patients recovering from high altitude pulmonary oedema (Roy et al, 1965). It would be of interest to know the changes in total blood volume as well but this was not measured in the present study. There appears to be only one study in the literature in which such a measurement was made and the author reported an increase in total blood volume (Bonnycastle, 1942). However, further studies are desirable before any firm conclusions can be drawn about the changes in total circulating blood volume.

Changes in Left Ventricular Performance: Both left ventricular stroke work and mean pulmonary wedge pressure decreased in three subjects and increased in one subject of group I. In the remaining two subjects the mean pulmonary wedge pressure decreased while stroke work did not alter significantly (Fig. 70). Although individual variations were observed, changes in mean stroke power index and mean ejection flow index were not significant for the group as a whole. On the other hand mean pulmonary wedge pressure decreased significantly in most subjects. Figures 70 and 71 are a plot of the mean values of left ventricular stroke work and mean stroke power index during the control period and each of the three post-injection periods, in individual subjects. The interpretation of these changes is discussed later in this section.

The left ventricular minute work decreased significantly in group I due mainly to a decrease in the cardiac output. The systolic minute pressure-time index, also, decreased, while the diastolic minute pressure-time index increased. The magnitude of these changes was small so that their functional significance would appear to be little, if any.

Group II

The most significant "delayed effects" of morphine in patients with left ventricular failure were the changes in pulmonary circulation. Although apparently variable changes were seen in other haemodynamic parameters, a coherent pattern is revealed when these are examined in the light of changes in the pulmonary circulation. For this reason the changes in pulmonary circulation will be discussed first.

Changes in the Pulmonary Circulation: A significant decrease in mean pulmonary wedge pressure with (three patients) or without (one patient) a similar decrease in mean pulmonary artery pressure occurred in all four

patients of group II. This was apparent within 3 minutes of the injection of morphine in two patients and only after 7 and 25 minutes in the other two. The average decrease in mean pulmonary wedge pressure, during post-drug periods 2, 3 and 4 (i.e. 10 to 60 minutes) in the group as a whole varied between 3.2 (9.7%) and 7.0 (21.1%) mm.Hg, while the maximum average decrease observed in individual patients during these periods varied between 3.7 (13.5%) and 12.2 (27.4%) mm.Hg. Associated with these changes was the decrease in cardiopulmonary blood volume which, during post-drug periods 2, 3 and 4, averaged between 19 (3.5%) and 31 (5.7%) ml./sq.m. for the group as a whole. Because of the relatively large variations between successive measurements of cardiopulmonary blood volume in one patient (T.H.) the average figures of this measurement during post-drug periods 2 and 3 were not significantly different from the control mean, but even in this patient a general trend towards a decrease can be seen in Fig. 47.

The author is well aware of the limitations in the assessment of changes in cardiopulmonary blood volume as estimated in the present study. Changes in volume of the left ventricle or left atrium could affect this measurement in either direction, and the possible loss of indicator particles in the pulmonary oedema fluid could introduce unpredictable errors. However, corroborative evidence suggesting that the observed changes in cardiopulmonary blood volume were in fact "real" and mainly due to changes in pulmonary blood volume is provided by the report of Roy et al (1965) who found a decrease in pulmonary blood volume (left atrium and ventricle excluded) after an intravenous injection of morphine given to four patients who had recovered from high altitude pulmonary oedema. It must, however, be noted that the precise nature of

high altitude pulmonary oedema is not known and that there is no evidence that this is due to left ventricular failure (Singh, 1965).

In addition to the changes in pulmonary blood volume mentioned above, a relatively small decrease in mean left atrial pressure was also observed by Roy et al (1965) in three of their four patients, but the authors did not consider the latter changes as having any physiological significance. However, from the information provided, the subjects of Roy et al (1965) had a fairly normal "haemodynamic state" at the time of their study, and would therefore be comparable to groups I and III of the present study. It will be recalled that in group I a relatively small but significant decrease in both mean pulmonary wedge pressure and cardiopulmonary blood volume was observed, while only the latter change was consistently found in group III.

The only other study, apart from the present report, in which the changes in pulmonary circulation following an injection of morphine to patients in left ventricular failure have been reported, is that of Fejfar et al (1959). In the course of their studies on acute pulmonary oedema of cardiac origin, these workers found a fall in mean pulmonary artery pressure after the administration of morphine. Detailed data was provided for only two of the nine patients studied and from these a striking fall in mean pulmonary wedge pressure is obvious in one patient but the authors did not make any comment about this.

The significance of the observed changes in pulmonary circulation (groups I and II) in relation to the syndrome of left ventricular failure is obviously paramount. Dyspnoea is the primary complaint of such patients. The mechanism of dyspnoea is a controversial subject and as yet unresolved, but evidence is accumulating to suggest that "length:tension

inappropriateness" due to competing receptors in the lungs may be, at least in part, responsible (Campbell and Howell, 1963; and Bates and Christie, 1965). It has been repeatedly demonstrated that the compliance of the lungs is markedly reduced in left ventricular failure (Christie and Meakins, 1934; Frank et al, 1957; Sharp et al, 1958; and Turno and Fishman, 1959) and improvement towards normal figures has been shown on recovery from pulmonary oedema (Sharp et al, 1958). However, in a later study by the last-named workers (Sharp et al, 1961) no significant changes in pulmonary compliance were seen, despite clinical improvement, following the administration of intravenous morphine to three patients who were in pulmonary oedema due to left ventricular failure. These workers did not make any haemodynamic measurements, and it is the opinion of the present author that further studies on the effects of morphine on ventilatory mechanics in patients with left ventricular failure should be made before any firm conclusions in this regard can be drawn. There is little doubt, on the basis of evidence from the present study, that a favourable situation is produced in these patients after intravenous administration of morphine which should lead to a decrease in the transudation of fluid into the alveoli as well as interstitial tissues of the lungs. If dyspnoea in patients with left ventricular failure is due to their difficulty in ventilating "turgid" lungs it follows that with improvement in the latter, dyspnoea should be relieved. Although these arguments are speculative in nature and lack direct experimental proof, they nevertheless indicate deficiencies in existing knowledge and possible avenues of future research.

Collateral evidence from two sources provides some support for the hypothesis that morphine produces dynamic changes which lead to a reduction

in the pulmonary oedema fluid in acute left ventricular failure. Firstly, Halonen and Hakila (1952) have shown that morphine prevents the pulmonary oedema that follows the administration of adrenaline to guinea pigs. These workers assessed pulmonary oedema from the wet weight of the lungs of the animals and also obtained histological confirmation of their findings.

The second piece of evidence comes from the changes in the blood gases and pH observed in the present study in patients of group II. In three of the four patients a decrease in PO_2 associated with an increase in PCO_2 and a reduction in pH was observed after the administration of morphine. However, in the fourth patient (G.C.), while the PCO_2 increased and pH decreased, a progressive increase in PO_2 occurred from 20 minutes onwards (Fig. 65). The relevance of these findings to the statement made above necessitates a brief digression to consider the mechanisms of changes in blood gases in left ventricular failure.

Abnormalities of blood gas tensions have been repeatedly demonstrated in patients with acute left ventricular failure and pulmonary oedema from other causes (Ebert, 1961). The low levels of PCO_2 with or without an elevated pH frequently seen in this disorder can be adequately explained on the basis of hyperventilation. Similar changes in PCO_2 and pH were found during the control period in the three patients of group II who had clinical evidence of acute left ventricular failure and pulmonary congestion. However, no entirely satisfactory explanation has been forthcoming for the arterial hypoxia which has also been frequently observed in this condition by those who have made the relevant measurements (Saunders, 1965). An increase in the A-a (Alveolo-arterial) gradient has been demonstrated in some of these patients and the failure to find

the expected rise in the PO_2 on administration of 100% oxygen suggests that abnormalities of the ventilation-perfusion relationships (V/Q) are, at least in part, responsible (Saunders, 1965).

In the present study significant reductions in PO_2 during the control period were found in two of the four patients of group II.

Following the administration of morphine changes in PCO_2 and pH in all four patients of group II were similar to those observed in groups I and III and these would be explicable on the basis of the alveolar hypoventilation that is produced by morphine (vide supra). Similarly the observed decrease in PO_2 in three of the four patients could also have been caused by the same mechanism. On the other hand the progressive rise in PO_2 in the fourth patient of this group, in the face of alveolar hypoventilation (rising PCO_2 and declining pH), can only be explained by a decrease in the venous-admixture effect or increased diffusion of oxygen across the alveolar-capillary interface, and thus constitutes further evidence of "improved" lung function following the administration of morphine to patients in acute left ventricular failure. That a similar increase in PO_2 was not observed in the other two patients, who were also in acute left ventricular failure, and showed similar changes in pulmonary pressures and cardiopulmonary blood volume, may have been due to several reasons. For instance the precise nature of the V/Q abnormalities in acute left ventricular failure is not known and it may be that the relative contribution of various factors determines the response to therapy. Again the time taken for the oedema fluid to be cleared from the alveoli and interstitial tissues of the lungs is not known, and this may well vary between individual patients. Other possibilities could be added to enlarge the list but it is sufficient for the present to indicate

that the data obtained from the present study demonstrate that morphine produces changes in the pulmonary circulation which have an undoubted bearing on the therapeutic efficacy of this drug in the treatment of acute left ventricular failure.

Whatever the precise cause of dyspnoea in left ventricular failure, there is little doubt that it is associated with the raised mean pulmonary wedge or left atrial pressure. Any investigator undertaking routine cardiac catheterisation will vouch for this fact. Formal proof has been obtained by Mauck et al (1964) who have shown a very good correlation between the level of mean pulmonary wedge pressure and the onset (average pulmonary wedge pressure 34 mm.Hg) or disappearance (average pulmonary wedge pressure 21 mm.Hg) of dyspnoea. Similar changes in mean pulmonary wedge pressure during pulmonary oedema have also been noted by Fejfar et al (1959) and Finlayson et al (1961). Sarnoff et al (1953) reported an increase in mean left atrial pressure from 1 to 21 mm.Hg in dogs when pulmonary oedema was produced by intracisternal (cisterna magna) injection of thrombin and fibrinogen. Excessive minute ventilation at rest and increased ventilatory response to exercise in patients with heart disease has also been shown to correlate best with the level of mean pulmonary wedge pressure (Donald, 1959; and Gazetopoulos, 1966), although these patients do not always complain of dyspnoea.

The mechanism involved in the production of the observed changes in pulmonary circulation following the injection of morphine, which were most marked in patients with left ventricular failure and less marked though definitely demonstrable in normal subjects, is not known. However, on the basis of available evidence, both from the present study and reports of other workers, a hypothesis concerning the mechanism of action of

morphine will be developed in the course of the ensuing discussion.

The decrease in cardiopulmonary blood volume associated in some cases with a fall in mean right atrial pressure suggests a shift of blood from the central reservoir to the periphery. Since the systemic venous bed is a large capacity system, which is influenced by a variety of factors, it seems possible that venodilatation may well be the underlying mechanism leading to the beneficial effects of morphine in left ventricular failure. Although occasional references to this possibility can be found in the literature (Lurie, 1963) no attempt seems to have been made to test the hypothesis formally. However some support in favour is provided when the haemodynamic changes following alterations in venous return induced by mechanical means (balloons) or pharmacologic agents are considered. A surprising similarity is found between the results of the present study and the haemodynamic effects produced by impeding the venous return (by an inflated balloon in the inferior vena cava) in human subjects as reported by Ross and Braunwald (1964). These authors noted a fall in left ventricular end-diastolic pressure, cardiac output, stroke volume and left ventricular stroke work in five normal subjects. On the other hand, the only marked change in nine patients with varying degrees of left ventricular dysfunction (as assessed clinically) was a decrease in left ventricular end-diastolic pressure. No measurements of pulmonary blood volume were made but it must have, almost certainly, decreased. The conclusion arrived at by these workers was that patients in left ventricular failure are operating on the flat part of a "Starling curve" while normal subjects are on the "ascending limb" of this curve, so that a comparable decrease in filling pressure does not affect the function of a failing ventricle while the external work performed by a normal ventricle

is reduced. Essentially similar results were reported in earlier studies on the effects of phlebotomy or induced venous congestion of limbs in patients with heart failure (McMichael and Sharpey-Schaffer, 1944; Warren et al, 1945; and Howarth et al, 1946). Although these latter studies made a significant contribution to the understanding of cardiac function at the time, they did not include a study of left ventricular performance. However, an increase in cardiac output following this procedure has been occasionally found in patients with congestive cardiac failure (Howarth et al, 1946).

The importance of peripheral venous system in the regulation of venous return and the pulmonary blood volume is now recognised (Johnson, 1951; Asmussen and Nielsen, 1955; and Ebert, 1963; Guyton, 1963; and Gauer and Thron, 1965). Autonomic control of the systemic veins is predominantly mediated through their sympathetic innervation (Alexander, 1963). The effectiveness of ganglion blocking agents in the treatment of pulmonary oedema due to left ventricular failure has been repeatedly pointed out (Luisada and Cardi, 1956). Their beneficial effect was until recently considered to be due to the systemic hypotension they produce (Hayward, 1955). While this will undoubtedly reduce the load on the left ventricle, the venodilator effect of these drugs leading to a redistribution of the circulating blood volume has been recognised only recently as the more probable mechanism responsible for their therapeutic effectiveness (Fries et al, 1953; and Aviado, 1960).

The capacity of the systemic arterial bed is only a fraction of that of the venous bed (Alexander, 1963). Small changes in the calibre of the arterioles will produce a profound change in blood pressure (Poiseuille's Law) but this is unlikely to result in a major shift of blood volume between vascular compartments. On the other hand, the systemic venous

bed due to its highly compliant and capacious nature is well adapted for this purpose.

It is of interest, in this connection, to note the results of a recent study on the effects of nitroglycerin and amyl nitrite on peripheral vessels and cardiac output. While both have been shown to have a potent vasodilator action on the arterioles leading to hypotension, amyl nitrite produces venoconstriction but nitroglycerin causes venodilatation (Mason and Braunwald, 1965). Cardiac output increases after the former drug (Perloff et al, 1963) and decreases following the administration of nitroglycerin (Williams et al, 1965).

The decrease in pulmonary vascular pressures, in particular mean pulmonary wedge pressure, and cardiopulmonary blood volume together with the reduction in cardiac output observed in the group of normal subjects in the present study, could be explained on the basis of a venodilator action of morphine. Failure to observe a consistent decline in mean right atrial pressure is not definite evidence against this hypothesis. That the changes in the pulmonary circulation were more marked in patients with left ventricular failure may have been due to the enhanced tone and responsivity of the systemic veins, a well known feature of this disorder (Sharpey-Schaffer, 1961). Alternatively, this quantitative difference in the response of the two groups may have been, in part, due to the fact that patients in left ventricular failure were studied in a propped up position as opposed to subjects of groups I and III who were all recumbent during the investigation.

Collateral evidence in favour of this hypothesis is also provided by the observation of orthostatic hypotension following intravenous morphine (i.e. that morphine has a venodilator effect). During the earlier stages

of the present study this was an invariable observation so that in the later stages patients were specifically instructed not to get up from bed for at least a couple of hours after completion of the investigation. It may be argued that the stress of the investigation and prolonged recumbency may have contributed to this phenomenon but none of the scores of patients on whom similar investigations, for as long or even longer periods, have been carried out in this laboratory have had a similar experience. In fact the experience was so unique as to have prompted spontaneous comments from the attendant nursing staff who have had several years experience in the laboratory. Orthostatic hypotension following injection of morphine has also been observed by several other workers and was most convincingly demonstrated by Drew et al (1946) when eleven of their 23 subjects "fainted" on being tilted to a 75° head up position while only two of these had a similar experience prior to the administration of morphine. These workers proceeded to bandage the legs and thighs in nine of the eleven "fainters" following which only two subjects fainted when tilted up for a third time. The prophylactic effectiveness of bandaging of the lower limbs is analogous to the similar effect seen after immersion of legs in water (or wearing of suits) in patients who have orthostatic hypotension. There is little doubt that either of these procedures is effective by virtue of the resulting increase in the extramural pressure on the limb veins. It is now accepted that orthostatic hypotension is caused, at least in part, by a failure of reflex venoconstriction on assuming the upright posture (Bevegård et al, 1962; Page et al, 1955; Ebert, 1963; Lurie, 1963; and Folkow and Mellander, 1964).

Changes in Left Ventricular Performance: Since direct evidence in support of this proposed venodilator action of morphine is lacking, it is necessary to examine any other possibilities that could explain the observed haemodynamic changes. The only alternative mechanism that could be invoked is that morphine improves myocardial contractility which in turn leads to a decrease in left ventricular filling pressure (mean pulmonary wedge pressure - Chapter III) and cardiopulmonary blood volume. It is the submission of the present writer that such a possibility is not borne out by the facts observed.

There is only one report in the literature which has advanced positive evidence in support of an isotropic action of morphine. In an intact dog preparation, Vasko et al (1966) have shown that administration of morphine (1 mg/kg) results in an increase in right ventricular contractile force and a "shift to the left" of left ventricular function curves. This effect was blocked by dichlorisoproterenol (a β -receptor blocking agent) but not by stellate ganglionectomy so that the conclusion of these workers was that morphine improves myocardial performance by virtue of "sympatho-adrenal discharge", presumably from the adrenal medulla. No direct measurements of plasma catecholamine concentrations were made but there is supportive evidence in the literature for such an action of morphine in dogs, mediated through supraspinal autonomic centres, which also leads to hyperglycaemia (Reynolds and Randall, 1957).

There is, however, no evidence available at present in support of a similar action in man. As already pointed out hyperglycaemia is not a consistent finding in man, nor was it found in the present study. Previous studies on isolated mammalian hearts have shown an initial but transient stimulant action followed by a sustained depression of both

frequency and amplitude of contraction (Gruber and Robinson, 1929; Schmidt and Livingstone, 1933; and Krueger et al, 1941) but the adrenal medulla was obviously excluded in these studies.

In the present study left ventricular stroke work and mean stroke power index either decreased or did not alter significantly in the four patients in left ventricular failure while the mean pulmonary wedge pressure consistently decreased in all patients. Similar changes were also observed in the group of normal subjects (group I) with one exception. While mean ejection flow index did not change consistently in normal subjects, a small but significant increase occurred in the patients of group II. Figs. 70, 71, 73 and 74 are a plot of the average values of stroke work and mean stroke power index during the control period and each of the successive post-injection periods. Such a plot is one form in which changes in myocardial contractility can be represented. At first glance an improvement in myocardial contractility, as generally understood (Chapter I), is apparent during the three post-injection periods (2, 3 and 4) under discussion. It will be seen that in both groups of subjects this is entirely due to a decrease in mean pulmonary wedge pressure.

According to the "Frank-Starling Law" the tension developed by the myocardium is a function of its initial length which in the case of a ventricle is proportional to its volume. Assuming for the moment that the pressure-volume curve of the left ventricle is linear (which it is not) any increase in its end-diastolic pressure (all other influences being constant) will result in an increase in end-diastolic volume which, in turn, will be manifest as either increased stroke work or stroke power index or the first differential of the ventricular pressure pulse or any

combination of these (Chapter I). The converse of this is also true. If therefore the end-diastolic pressure (and hence volume) be reduced, all these functions will show a decline. In neither instance can it be said that the intrinsic contractile properties of the ventricular muscle have changed in so far as no more or no less tension is generated for the same muscle length. Such an inference can only be drawn when a definite change in the slope of the ventricular function curve is demonstrated.

The data from the present study reveals a decline in mean pulmonary wedge pressure as well as left ventricular stroke work in the majority of normal subjects (group I). In the only exception (G.P.) to this both stroke work and mean pulmonary wedge pressure increased. As already pointed out similar results were obtained by Ross and Braunwald (1964) following mechanical reduction in venous return. In both instances (present study and that of Ross and Braunwald) the left ventricle most probably "moved down" (or up) on its own "function curve" (Chapter I) without any change in its intrinsic contractile properties. The difficulties in defining the unique "function curve" of any single ventricle in a human being, without imposing graded stress, are well recognised. The impression given by Figs. 70, 71, 73 and 74 is evidence of such difficulties. However, on the basis of available information, there is no evidence of improved left ventricular function following administration of morphine to the group of normal subjects. It is of interest to note the parallel increase in mean pulmonary wedge pressure in the only normal subject in whom stroke work increased.

Before proceeding to consider the results of patients in group II the statement about the pressure-volume curve of the left ventricle made

above must be modified since it is well established that the actual shape of this curve (as with all hollow organs) is that of a rectangular hyperbola (Braunwald et al, 1960). Patients in left ventricular failure are generally operating on the steep limb of their pressure-volume curve (Braunwald, 1965) so that relatively large changes in end-diastolic pressure result in small changes in end-diastolic volume.

From studies on isolated papillary muscles it has also been shown that the length-tension curve of these patients is depressed and relatively flattened (Chidsey et al, 1966).

In the present study very high mean pulmonary wedge pressures were found during the control period in three patients with left ventricular failure. Therefore, these patients were, in all probability, also operating on the steep limb of the ventricular pressure-volume curve.

Except for patient R.T. (only moderately elevated mean pulmonary wedge pressure) it is unlikely that the decrease in mean pulmonary wedge pressure produced any significant changes in end-diastolic volume. For this reason, therefore, it is not surprising that no marked changes in either stroke work, mean stroke power index, or mean ejection flow index were observed in spite of the fall in mean pulmonary wedge pressure. The first differential of the aortic pressure pulse, for what it is worth, declined in both groups.

The decrease in left ventricular minute work as also systolic and diastolic minute pressure-time indices observed in most patients of group II was due to the decrease in aortic blood pressure. Little further insight into the effects of morphine on left ventricular performance is gained by any further consideration of these changes.

It is therefore obvious from these arguments that there is no objective

evidence in either group of subjects (normal subjects and patients with left ventricular failure) to support the possibility of an inotropic action of morphine. The results can be much more adequately explained if the possibility of venodilatation is accepted.

Before closing this part of the discussion it may be pointed out that various parts of the central nervous system have been shown to be associated with marked circulatory changes (Loefving, 1961; and Hoff et al, 1963) which, in all probability, involve the capacitance vessels as well as other structures (Folkow and Mellander, 1964). The studies of Sarnoff et al (1953), who produced pulmonary oedema in dogs by the injection of thrombin and fibrinogen into the cisterna magna, are of particular interest in this regard. It may well be that the venodilator action of morphine is mediated through its action on the central nervous system. Unfortunately, little definite information about the precise loci of action of morphine is available (Wikler, 1950).

Changes in the Systemic Circulation: Following the postulated reduction in venous return, the cardiac output would be expected to fall and this was observed in most subjects in group I (and III). In the only two exceptions to this, the possibility of a reflex increase in cardiac output following the secondary decrease in systemic vascular resistance has already been pointed out. The variable changes in cardiac output ("delayed effects") seen in the patients in left ventricular failure (group II) are best examined in the light of the observed changes in pulmonary circulation. A close look at Figs. 47 and 48 reveals that the cardiac output generally moved in an opposite direction to the changes in mean pulmonary wedge pressure except in patient T.H. It should be noted that in the last named patient the magnitude of the decrease in pulmonary wedge pressure was the

smallest in this group. It is of further interest to note the time course of these respective changes especially in patient A.S. The cardiac output in this patient remained low (after the initial decrease) for as long as the mean pulmonary wedge pressure remained at control levels or above. As the pulmonary wedge pressure decreased the cardiac output increased, admittedly only to control levels, in spite of a decrease in heart rate.

No consistent changes in stroke volume were seen in these patients of group II and this would be in keeping with the proposed hypothesis (vide supra).

Changes in whole body oxygen uptake were also variable although a significant decrease for the whole group was observed. The magnitude of this decrease was small and therefore unlikely to be of any physiological significance.

The secondary fall in mean aortic pressure that occurred in all patients of group II is difficult to explain. Thomas et al (1965) also found a fall in brachial artery pressure in most of their patients with acute myocardial infarction but without evidence of acute left ventricular failure (except one). They too considered this to be a more frequent occurrence than would be expected from the published reports on the effect of morphine in normal subjects. It may be that the arteriolar vasoconstriction (increased sympathetic activity) that is associated with acute left ventricular failure (or acute myocardial infarction) is partially reversed following the relief of pulmonary congestion, (or pain of acute myocardial infarction). Whether this hypotensive effect of morphine bears any relationship to a similar effect observed in two subjects of groups I and II is not clear from the data. If the relative frequency of its

occurrence is any indication of the underlying mechanism the two actions may be unrelated or partially so. It is also possible that the abnormal susceptibility of some patients to the hypotensive effects of morphine as seen in the two subjects of groups I and III may summate with the hypotensive effect consistently observed in patients with left ventricular failure, thus resulting in a profound fall in blood pressure; a phenomenon that has been repeatedly emphasised as a hazard in the clinical use of the drug (Drew et al, 1946; Altschule, 1953; Louisada and Cardi, 1956; and Thomas et al, 1965). This explanation would accord well with the fact that hypotension following clinical use of intravenous morphine in the supine patient is not invariable.

Haemodynamic Changes during Vomiting: The haemodynamic changes during vomiting were an interesting accidental finding in the course of the present study. A marked increase in oxygen uptake, cardiac output and mean aortic pressure associated with a decrease in systemic vascular resistance appear to be the more important changes. The mechanism of these changes is not known but the influence of the associated violent respiratory movements, comprising of rapidly successive Valsalva manoeuvres, would appear to be of some importance. It may be mentioned in passing that the precise mode of action by which morphine produces vomiting is not known. It is now recognised that vomiting is much more frequent in the upright posture than in the supine subject (Comroe and Dripps, 1948; Huggins et al, 1949; and Rubin and Winston, 1950). This was also observed in the course of the present investigation. While vasomotor disturbances leading to postural hypotension may be responsible (Huggins et al, 1949), it has been shown that vestibular function is also affected by morphine (Rubin and Winston, 1950). The latter seems the more probable cause of vomiting.

SUMMARY, CONCLUSIONS AND POSSIBLE AVENUES OF FUTURE RESEARCH

In conclusion, therefore, the present study documents for the first time the sequential haemodynamic changes following an intravenous injection of morphine. These can be broadly classified into two types of responses.

1. "Immediate effects" which were most pronounced within the first minute and pass off within 10 minutes. An increase in cardiac output and heart rate together with peripheral vasodilatation in some or all vascular territories were the principle features of these changes. Whole body oxygen uptake also increased in some subjects.

Evidence has been presented which suggests that morphine may exert a transient inotropic effect on the heart muscle at this time. However, these changes are transient and, therefore, do not appear to be of any therapeutic importance.

The precise mechanism of action of morphine leading to the "immediate effects" is not known but various possibilities such as the histamine liberating properties of morphine, a central stimulatory action or a direct peripheral effect on the heart and/or blood vessels need to be explored further. Evidence in support of each of these possible mechanisms of action has been indicated.

2. "Delayed effects" which may appear within the first 10 minutes of administration of the drug intravenously or be delayed for as long as 20 to 25 minutes. This action persists up to, at least, one hour which is the longest that all patients were studied for.

The most prominent and consistent change during this period was a decrease in the mean pulmonary wedge pressure and the cardiopulmonary blood volume, particularly in normal subjects and patients with left ventricular failure. The therapeutic value of this pharmacological action

of morphine has been discussed.

Subjects of groups I (normal subjects) and III (patients with mitral valve disease) showed a decrease in the cardiac output, while variable changes were found in patients of group II (left ventricular failure).

Left ventricular stroke work decreased in most subjects of group I (except one subject), but no significant changes in this parameter were found in patients of group II. Variable changes in left ventricular mean stroke power index and mean ejection flow index were observed in subjects of both groups I and II. Changes in left ventricular minute work generally followed the changes in cardiac output.

It has been concluded that the observed changes in the indices of left ventricular performance do not indicate an improvement in myocardial contractility in so far as the slope of the "left ventricular function curve" did not, probably, alter.

On the strength of the observed changes, and evidence from other reports, a hypothesis of the mechanism of action of morphine has been postulated. It has been suggested that these haemodynamic changes are best explained by a redistribution of the circulating blood volume leading to a decrease in cardiopulmonary blood volume and mean pulmonary wedge pressure. These changes were most marked in the group of subjects (left ventricular failure) in whom venous tone is known to be increased. A study designed to test this hypothesis would be desirable. Even with the limitation of the currently available techniques, it should be possible to confirm or refute this hypothesis.

On the basis of the observed changes in the systemic circulation it has been suggested that morphine produces vasodilatation leading to hypotension by what appear to be three separate mechanisms, involving some

or all regional vascular territories.

Firstly, a transient decrease in the systemic vascular resistance immediately after the injection of morphine ("immediate effects"), was observed in all subjects (except one) of groups I and III. This was a transient change and reversed within 10 minutes in all subjects. The possible mechanisms of this action have been discussed.

Secondly, some subjects appear to be "sensitive" to the drug, in some manner, and in these a secondary fall in the systemic vascular resistance and blood pressure was observed. Since this happened in only two of the ten subjects of groups I and III, it does not appear to be a common pharmacological action of the drug.

Thirdly, in patients who are under increased sympathetic stimulation (e.g. acute left ventricular failure) the frequency of prolonged hypotension was much higher than would be expected on the basis of published reports. A suggestion has been made that this is due to the symptomatic relief in these patients with consequent reduction in the background sympathetic discharge.

The major contribution of this study would appear to be that, for the first time, evidence has been presented which should provide a rational basis for the well known therapeutic efficacy of morphine in acute left ventricular failure.

The enigma facing all cardiologists, that morphine, a drug that depresses respiration, leads to hypoxia, hypercapnia and respiratory acidosis, and is reputed to have an antidiuretic action, should ever be effective in the treatment of left ventricular failure, would appear to have been resolved to a large extent. Of course, further work will be desirable to confirm the findings of this study, but at least the direction

of such search has been indicated. In the past, several views have been advanced to explain the therapeutic efficacy of morphine in left ventricular failure but all these have been attempts at reconciling conflicting evidence. Respiratory depression and relief from dyspnoea have been suggested as one such mechanism. While it is accepted that both changes do occur, it has been suggested that morphine relieves dyspnoea by a subtle change in the pulmonary circulation, i.e. by redistribution of the circulating blood volume, and not entirely by depressing the respiratory centre. To this extent therefore morphine stands in its own right as one of the drugs useful in the treatment of acute left ventricular failure. Several other drugs also produce respiratory depression but none of these have been shown to be effective in the treatment of left ventricular failure, nor indeed is their action on pulmonary circulation known at present.

CHAPTER V

HAEMODYNAMIC CHANGES DURING SUPINE LEG EXERCISE WITH PARTICULAR
REFERENCE TO LEFT VENTRICULAR PERFORMANCE, AND THE EFFECT OF
 β -ADRENERGIC BLOCK ON THESE CHANGES

The haemodynamic changes during dynamic exercise in man have been studied extensively. During the past decade or so detailed investigations with the aid of modern techniques have produced a mass of data, both from human and animal studies, which have helped to define fairly precisely the pattern of the circulatory response to exercise. These studies have also provided some insight into the various mechanisms that normally control cardiovascular function both at rest and during added strain. It is beyond the scope of the present study to review all the available data and only a brief summary of the currently accepted views is presented. For the most part the review is confined to studies performed on normal human subjects.

Changes in Systemic Circulation: It is well recognised that the increased metabolic demands during dynamic exercise, particularly the need for oxygen, are met by an increase in both the cardiac output and oxygen extraction per unit of blood (Asmussen and Nielsen, 1955; Donald et al, 1955; and Mitchell et al, 1958a). The cardiac output has been shown to increase linearly with the increase in oxygen uptake (Donald et al, 1955). More recent evidence, however, suggests that the relationship is linear only over the middle of the range from low levels of exercise to maximal exercise. It has been shown that at low levels of exercise the increase in cardiac output is small relative to the increase in oxygen consumption (Reeves et al, 1961; and Frick and Somer, 1964) and that a similar relationship obtains during maximal exercise (Åstrand et al, 1964). Thus the "true" shape of the oxygen uptake-cardiac output curve is probably sigmoid although in between the extreme ranges the relationship is linear. This accords well with the changes that have been observed in oxygen extraction per unit of blood.

The A-V oxygen content difference increases sharply at low levels of exercise while the curve gradually flattens out as the exercise load is increased (Donald et al, 1955; Wang et al, 1960; Reeves et al, 1961; and Frick and Somer, 1964). Presumably the relative flattening out of both cardiac output and oxygen extraction at maximal levels of exercise is related to the accumulation of oxygen debt.

The mechanisms underlying the increase in cardiac output during dynamic exercise have been a subject of controversy. For a long time it was believed that during exercise both heart rate and stroke volume increase proportionately (Krogh and Lindhard, 1912). Later conflicting reports from various laboratories appeared; some demonstrating an increase in stroke volume, while others failed to find any such increase during exercise (Riley et al, 1948; Dexter et al, 1951; Asmussen and Nielsen, 1952; Donald et al, 1955; Theilen et al, 1955; Freedman et al, 1955; and Barrett-Boyes and Wood, 1957).

These observations, together with the demonstration that the heart volume decreases during exercise lead to speculation about the importance of the "Frank-Starling" Law in the control of cardiac function particularly during exercise. A cross-section of the views prevailing at the time was published in the form of a symposium in *Physiological Reviews* (1955). However, it has now been established by several workers that the discrepancies between the various reports on the changes in stroke volume during exercise were mainly due to the different postures in which the subjects were studied (Rushmer, 1959). It is now known that during exercise in the supine position the stroke volume increases only minimally as compared to the marked increase that occurs when exercise is performed in the upright posture (Holmgren et al, 1960; Wang et al, 1960;

and Bevegård et al, 1963). Even the small increase in stroke volume that occurs initially during supine leg exercise has been shown to be due merely to the elevation of the lower limbs before actual exercise is undertaken (Frick and Somer, 1964). To this extent, therefore, the initial increase in stroke volume during supine leg exercise is a "spurious" response.

A small increase in the mean aortic pressure, both during supine and upright exercise, has been the usual finding of most workers. This has been shown to be mainly due to an increase in the systolic pressure while the diastolic pressure is more or less unaltered (Riley et al, 1948; Dexter et al, 1951; Donald et al, 1955; Theilen et al, 1955; Holmgren, 1956, Barratt-Boyes and Wood, 1957; Wang et al, 1960; Gorlin et al, 1964; and Epstein et al, 1965). The magnitude of the increase has also been shown to vary directly with the level of exercise performed (Donald et al, 1955; Holmgren, 1956; and Taylor et al, 1962).

A fall in the systemic vascular resistance, the magnitude of which is directly related to the level of exercise undertaken, has been consistently observed by all workers who have made the relevant measurements and calculations (Riley et al, 1948; Dexter et al, 1951; Donald et al, 1955; Barratt-Boyes and Wood, 1957; Bevegård et al, 1963; Taylor et al, 1962; and Epstein et al, 1965). This is presumably due to the vasodilatation that occurs in the exercising muscles.

Changes in Pulmonary Circulation: The changes in pulmonary circulation during dynamic exercise have also been well documented although fewer reports as compared to those concerning changes in the systemic circulation are available.

The usual finding has been a small increase in the mean pulmonary artery pressure at the onset of exercise and this persists for a few minutes

during the exercise (Donald et al, 1955; Barratt-Boyes and Wood, 1957; Sancetta and Rakita, 1957; Holmgren et al, 1960; Taylor et al, 1962; and Fishman, 1963). It has, however, been shown that part of the increase at the onset of supine leg exercise is related to the act of leg raising before the commencement of exercise. Furthermore, the increase in mean pulmonary artery pressure tends to level off with increasing loads of exercise, and if a particular level of exercise is maintained for long enough this pressure tends to decline and may even return to pre-exercise levels (Sancetta and Rakita, 1957). Thus the changes in mean pulmonary artery pressure would appear to be passively related to the increased pulmonary blood flow.

Only a few workers have measured the changes in the mean pulmonary wedge pressure, and a small increase in this measurement has been the usual finding (Dexter et al, 1951; Holmgren et al, 1960; Taylor et al, 1962; and Bevegard et al, 1963).

The findings with regard to the changes in pulmonary vascular resistance have not been consistent, but the consensus of opinion would appear to be that this decreases passively with the increase in pulmonary blood flow (Fishman, 1963).

The cardiopulmonary blood volume has been shown to increase during exercise in both the supine and upright posture (Mitchell et al, 1958b; and Braunwald and Kelly, 1960).

Variable changes in mean right atrial pressure have been observed by different workers but in general this either does not change or may decrease slightly (Asmussen and Nielsen, 1955; and Holmgren, 1956). The difficulties in the interpretation of the mean right atrial or central venous pressure changes in relation to venous return have been pointed out by Guyton (1963).

Changes in Left Ventricular Performance: There are only a few studies in the literature in which specific data pertaining to left ventricular performance during exercise in human subjects have been obtained. Much of the information on this subject has come from the elegant studies of Rushmer and his colleagues (1959) performed in dogs.

These authors have demonstrated an increase in myocardial contractility during exercise on the basis of increased stroke power and rate of change of pressure (dp/dt) at the same or even reduced end-diastolic volume. Similar findings in dogs were also obtained by Chapman et al (1959).

From their studies in man, Gorlin et al (1964 and 1965) have shown that during supine leg exercise the end-diastolic and end-systolic volumes of the heart usually decrease, while the mean systolic ejection rate increases. The coronary blood flow in their subjects increased and so did myocardial efficiency. However, in some subjects, both the end-diastolic volume and stroke volume increased. Their conclusions were that positive inotropic effects influence the cardiac response in a majority of instances while in some cases the increase in diastolic volume brings into play the "Frank-Starling" Law (Chapter: I).

Braunwald et al (1963) also found a decrease in both end-diastolic and end-systolic volumes of the heart during exercise in man. These studies therefore confirm the earlier observations of several groups of workers that the volume of the heart during exercise either does not change or even decreases (while its mechanical activity is augmented (Liljestrand et al, 1938; and Gauer, 1955 Braunwald et al., 1963; and Sonnenblick et al., 1965).

In this connection, it will be recalled that the mean pulmonary wedge and left ventricular end-diastolic pressures increase during exercise

(vide supra and Chapter:III) while the end-diastolic volume of the ventricle, on the basis of evidence quoted above, diminishes. This discrepancy is presumably due to changes in intrathoracic pressure (Gorlin et al, 1965) since there is no evidence that the compliance of the ventricular muscle is altered during exercise.

More specific evidence bearing on the changes in myocardial contractility during supine leg exercise has been obtained recently by Sonnenblick et al (1965). These workers have studied changes in the force-velocity relationships in unanaesthetised post-operative cardiac patients. With the use of silver-tantalum markers, high speed cineradiograms, and intraventricular pressure records they have been able to study instantaneous changes in the velocity of fibre shortening and relate these to the intraventricular pressure obtaining at that instant. They have shown that the velocity of shortening is augmented by about 69% during supine leg exercise and that changes in heart rate alone do not result in a similar increase in the velocity of shortening. The conclusion therefore is that myocardial contractility is markedly increased during exercise. These observations are discussed in fuller detail later.

The mechanisms underlying the cardiovascular adjustments during exercise are currently under scrutiny. The dominant role of the sympathetic nervous system is generally accepted (Rushmer, 1962). Evidence in favour of this view can be summarised as follows:

1. Stimulation of the stellate ganglia in dogs results in changes in ventricular performance similar to those observed during spontaneous exercise (Anzola and Rushmer, 1956).

2. Stimulation of discrete areas in the central nervous system, particularly in the hypothalamic region, results in haemodynamic changes which closely simulate those observed during exercise (Rushmer et al, 1959).
3. Exercise is characterised by differential vasoconstriction in various regional vascular territories (Chapman et al, 1948; Bishop et al, 1957 a and b). Since vasoconstriction is mediated via the sympathetic nerves increased sympathetic activity is implied.
4. Infusion of isoproterenol produces circulatory changes qualitatively similar to dynamic exercise (Rushmer et al, 1959) although quantitative differences have been demonstrated (Krasnow et al, 1964). It should, however, be pointed out that isoproterenol is not a naturally occurring amine though it has pharmacological properties similar to those of adrenaline, in particular the β receptor stimulating actions of the latter (vide infra).
5. Adrenergic blocking agents like guanethidine have been repeatedly shown to reduce the magnitude of the circulatory response to exercise (Taylor et al, 1962; and Kahler et al, 1962).

6. Patients with idiopathic postural hypotension show an inadequate pressor response so that in some cases the mean aortic pressure has been shown to fall during supine leg exercise and this can be corrected by infusion of catecholamines (Bevegård et al, 1962). It has also been demonstrated that these patients have other evidence of inadequate sympathetic activity (Gauer and Thron, 1965).
 7. The urinary excretion of catecholamines is markedly elevated during exercise (von Euler and Hellner, 1952).
 8. β -receptor blocking agents have been shown to modify the circulatory response to exercise in both animals and man. The evidence on this point is discussed in detail later in this Chapter.
- Ahlquist in 1948 distinguished between α and β adrenergic receptors on the basis of the relative pharmacological actions of various catecholamines. On this basis positive inotropic and chronotropic effects on the heart together with vasodilatation of the muscular, coronary and splanchnic vascular territories constitute the chief circulatory functions of β -receptors, while vasoconstriction is mediated by α - receptors. Isoproterenol belongs to the former class while nor-adrenaline is an example of the latter group. The distinction between the two receptor activities extends to other organ systems as well (Ahlquist, 1965). This division of adrenergic receptors is entirely functional and to date there is no evidence of an anatomical basis for this differentiation. Nevertheless the introduction of pharmacological agents that selectively block one or the other of these receptor actions lends support to this concept.

It is apparent from this distinction that the sympathetic control of the cardiovascular response during exercise should be predominantly mediated through β - receptors. With the recent introduction of pharmacological agents that selectively block β - receptor activity it has become possible to test this hypothesis. It was, therefore, felt desirable to study the haemodynamic changes during supine leg exercise with particular reference to changes in left ventricular performance and also the effect of pharmacological β - receptor block on these. The present study was undertaken with this in view.

Propranolol has been shown to have selective β - receptor blocking properties and is devoid of the side-effects that have been reported with the other two agents of this class, namely dichloroisoproterenol and pronetholol (Black et al, 1964). It was, therefore, decided to use propranolol in the present studies.

Of the two naturally occurring sympathetic transmitter substances, namely adrenaline and nor-adrenaline only the former has both β and α receptor activities (Ahlquist, 1948). It is, therefore, more appropriate to use the term " β -adrenergic block" than " β -sympathetic block". However, either of these terms have been used by various authors and in the present study the two terms have been used interchangeably.

METHODS

The haemodynamic changes during supine leg exercise were studied in four normal male subjects. The clinical diagnoses and anthropometric data of these subjects are given in Table 48.

Exercise was performed on a bicycle ergometer coupled to the foot of the table on which the patients were lying. The work load could be set on this ergometer by tightening the friction belt and was indicated on a dial

calibrated in arbitrary units. No attempt was made to quantitate the amount of work done, this being assessed in terms of the whole body oxygen uptake as obtained from the data. From previous experience in the laboratory, it was known that a dial setting of 1 to 1.5 provided a light load equivalent to an oxygen uptake of roughly between 300 and 400 ml./min./sq.m. while the corresponding oxygen uptake at a dial setting of 2.5 to 3 was usually 500 to 700 ml./min./sq.m. The number of revolutions in unit time was held constant at any level of exercise by means of a differential gear system driven by a constant speed electric motor. Any variation in speed was indicated by the movement of a pointer which was within easy sight of the patient who was instructed to regulate the speed of pedalling so as to hold the pointer stationary. The subjects were familiarised with the procedure on the day before the investigation.

Two levels of exercise, light and moderately heavy, were chosen so as to study the haemodynamic changes during graded exercise. The actual work load at each level of exercise was determined at the time of training by the ability of each subject to maintain a given level of exercise for at least 5 minutes without undue distress or exhaustion. These were not, therefore, comparable between subjects.

The effect of β -adrenergic block, obtained with propranolol, on the circulatory response to supine leg exercise was also studied in the same four subjects. The details of the experimental protocol are shown in Fig. 75. Briefly, each subject performed exercise first, the light load preceding the heavier one, but without any break between the two levels of exercise. The initial inertia of the ergometer was overcome with help from a member of the attendant staff. Each level of exercise, designated as exercise 1 (light load) and 2 (moderately heavy load) was performed for exactly 6 minutes. Following exercise, a recovery period of at

EFFECT OF β -ADRENERGIC BLOCK ON HAEMODYNAMIC RESPONSE TO SUPINE LEG EXERCISE

PLAN OF INVESTIGATION

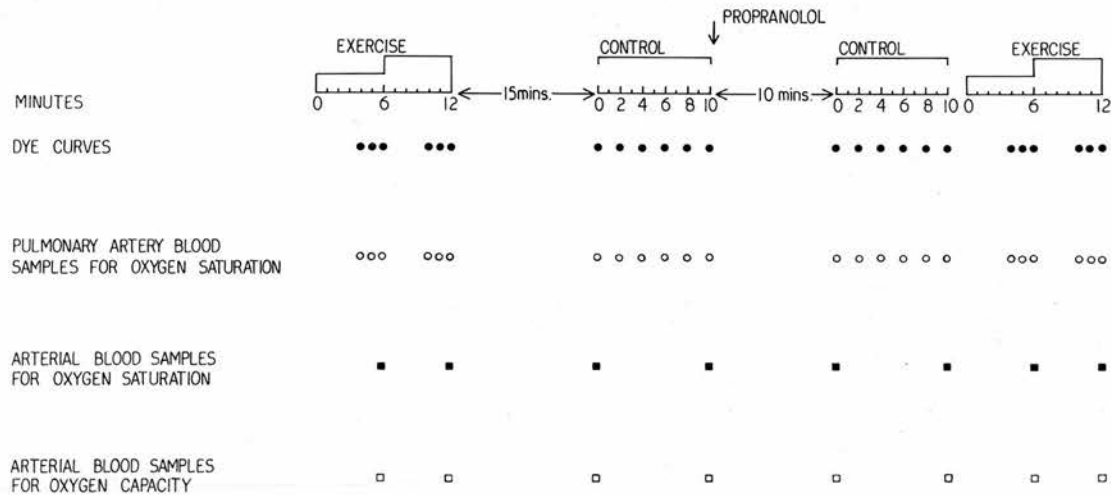


Figure 75

Effects of β -adrenergic block on the haemodynamic response to supine leg exercise. Plan of investigation. Injection of Propranolol given over a period of 5 minutes and another 10 minutes allowed to elapse before recording the second set of resting measurements.

least 15 minutes was allowed before resting measurements were obtained over a period of 10 minutes. On the basis of the report by Donald et al, (1954) and Taylor et al (1962), 15 minutes was thought to be a sufficient length of time during which all the haemodynamic variables return to resting levels. Immediately after the control resting measurements were obtained, propranolol* (10 mg. diluted in 10 ml. of saline) was injected slowly into the right atrium through the appropriate lumen of the cardiac catheter. The injection was given over a period of 5 minutes while the electrocardiogram and blood pressure were continuously monitored. To ensure full pharmacological action of the drug, a further 10 minutes were allowed to elapse before resting measurements were repeated during the succeeding 10 minutes. After this, the subjects again performed supine leg exercise at the same two work load as had been used previously, i.e. during the control measurements.

This experimental design may be criticised in so far as during the control period exercise was performed before the resting measurements were obtained, while the resting measurements after β -adrenergic block preceded the exercise. Previous experience in this laboratory (unpublished observations) has shown that the cardiac output following recovery from exercise is at a lower level as compared with the pre-exercise resting measurements. The reason for this is not clear. However, it was felt that in order to have two strictly comparable resting periods before and after β -adrenergic block, these should be spaced as close to one another as possible and certainly without interposing any events that could alter the "haemodynamic state" of the individual. It seems unlikely that the assessment of changes during exercise could have been influenced in any significant manner by this experimental design. On the other hand, it

* Courtesy of Imperial Chemical Laboratories.

offered the advantage of having two sets of resting measurements, with only a brief interval between them, on the same individual without prolonging the investigation unduly.

Vascular pressures and the electrocardiogram were continuously recorded throughout the exercise and rest periods. Cardiac outputs were determined at each minute during the last 3 minutes of the exercise period and at alternate minutes during the rest periods. Mixed venous blood was obtained at the same times as the cardiac outputs while arterial blood samples were obtained during the 6th minute of each period of exercise and also at the beginning and end of each rest period. It has been shown previously that a reasonably "steady state" is achieved within about 2 minutes of starting exercise (Donald et al, 1955). For this reason, measurements obtained only during the last 3 minutes of each level of exercise have been analysed. Thus, 3 consecutive, minute by minute, sets of observations were available in each of these periods. Resting measurements, both before and after β -adrenergic block, were obtained over a period of 10 minutes. Detailed analysis of the aortic pressure pulse was carried out on the short strips of this pressure, immediately preceding each dye curve, recorded at a paper speed of 13.54 cm./sec.

Details of the techniques used and the variables, both primary and derived, thus obtained are given in Chapter II.

Statistical analysis of the data was carried out by the conventional methods of comparing the means of small samples, and taking into account the differences between the variances of the means wherever these were demonstrated to be significant by the F test. In individual patients, the mean and standard deviation of each variable was calculated separately from the data obtained from resting measurements and during each of the two

exercise periods both before and after β -adrenergic block. For each variable, the significance of the difference between the means of the two sets of resting observations (i.e. before and after β -adrenergic block) was assessed in each subject as well as for the whole group by the "Student's" t test. Since the changes during exercise in most variables were distinct and of considerable magnitude, it was not deemed necessary to undertake any formal statistical treatment and the results in individual subjects as well as for the group have been expressed only as percentage changes as compared with the mean of resting observations. However, the changes in some variables (e.g. mean aortic pressure) were small so that formal statistical analysis for these was carried out again by the "Student's" t test. Further, the significance of the percentage changes from the resting mean at corresponding levels of exercise before and after β -adrenergic block was assessed by the t test on differences between each of such pairs of observations.

RESULTS

The detailed data obtained from each subject are given in Tables 49 to 52. Observations bearing on the systemic and pulmonary circulations are presented in part A of these tables while more specific observations concerning left ventricular performance are given in part B of each table. A summary of the data together with the results of some of the statistical analyses are given in Tables 53 to 56. A brief description of the results follows. The changes during exercise before the administration of propranolol will be dealt with first (A). This will be followed by a comparison of the resting observations obtained before and after β -adrenergic block (B). Lastly, the exercise responses at equal work loads before and after β -adrenergic block will be compared (C). All percentage figures

referred to in the text and given in the Tables are relative changes compared with the corresponding resting average unless otherwise stated.

A. Haemodynamic changes observed during supine leg exercise before β -adrenergic block:

Oxygen Uptake (Fig. 76). The resting oxygen uptake was within normal limits in each subject, the average value for the group being 139 ± 0.7 (S.E.) ml./min./sq.m. (Table: 53). During exercise 1 the average oxygen uptake was 352 ± 3.9 (S.E.) ml./min./sq.m., an increase of 153.2% over the mean of the resting values; and during exercise 2 the corresponding figure was 534 ± 6.0 (S.E.) which amounted to an average increase of 284.2% from the mean of the resting values (Table: 53). Although the design of the experiment did not require the subjects to perform equivalent levels of exercise the results obtained show relatively small variations in oxygen uptake between the subjects at each of the two levels of exercise.

A-V Oxygen Content Difference (Table:53) increased by 62.0% during exercise 1 and 105.5% during exercise 2 (Table: 53). Both the increase during exercise 1 and the difference between the average values of exercise 1 and 2 were statistically significant ($p < 0.001$).

Cardiac Output (Figs. 77 and 78) increased in all subjects during exercise 1 and a further increase was observed during exercise 2. The average resting cardiac output in the group was 3.21 ± 0.032 (S.E.) l./min./sq.m. and the corresponding figures during exercise 1 and 2 were 4.98 ± 0.074 (S.E.) l./min./sq.m. and 5.86 ± 0.105 (S.E.) l./min./sq.m. respectively. The percentage increases from the mean resting cardiac output were 55.1 and 82.6 during exercise 1 and 2 respectively (Table: 53). The difference between the mean values of exercise 1 and 2 was significant ($p < 0.01$).

CHANGES IN OXYGEN UPTAKE DURING SUPINE LEG EXERCISE BEFORE AND AFTER
 β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

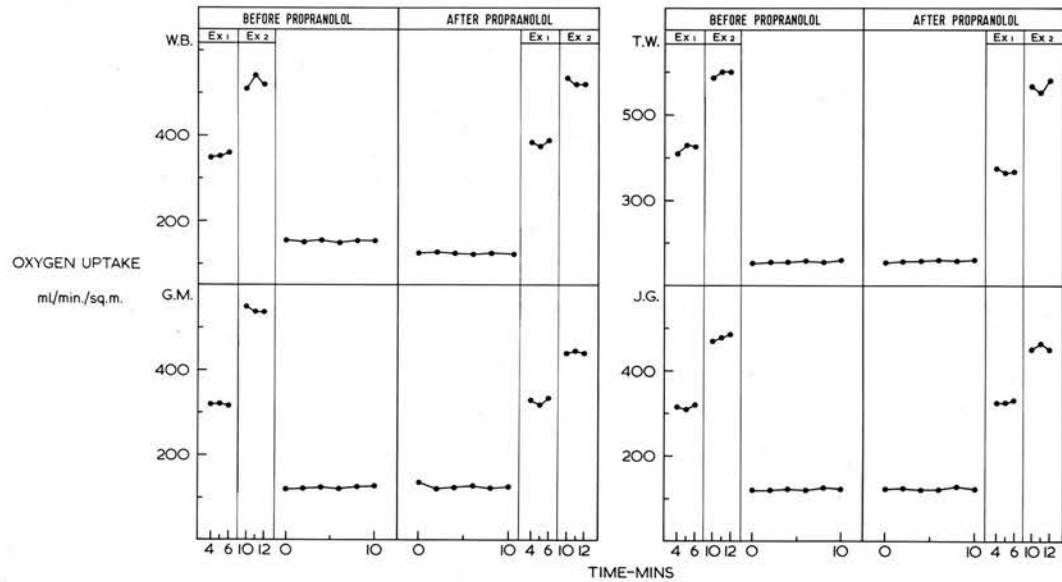


Figure 76

Changes in oxygen uptake during supine leg exercise before and after β -adrenergic block in 4 normal subjects.

CHANGES IN THE SYSTEMIC CIRCULATION DURING SUPINE LEG EXERCISE BEFORE AND AFTER
 β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

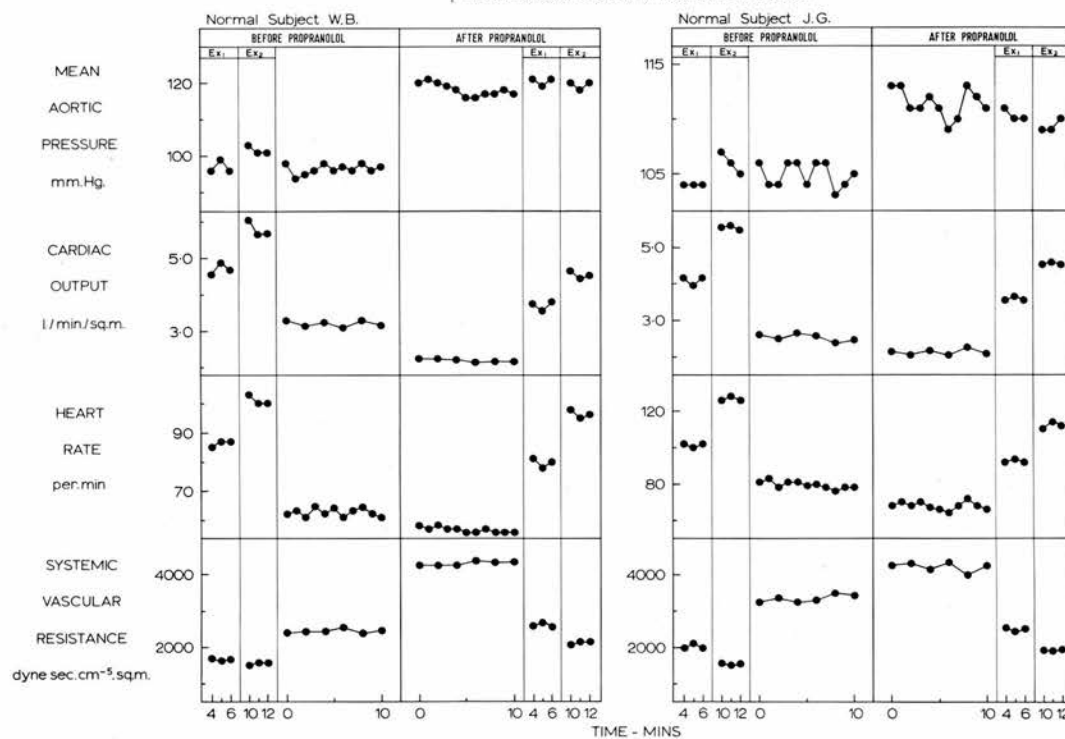


Figure 77

Changes in the systemic circulation during supine leg exercise before and after β -adrenergic block in normal subjects W.B. and J.G.

CHANGES IN THE SYSTEMIC CIRCULATION DURING SUPINE LEG EXERCISE BEFORE AND AFTER
 β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

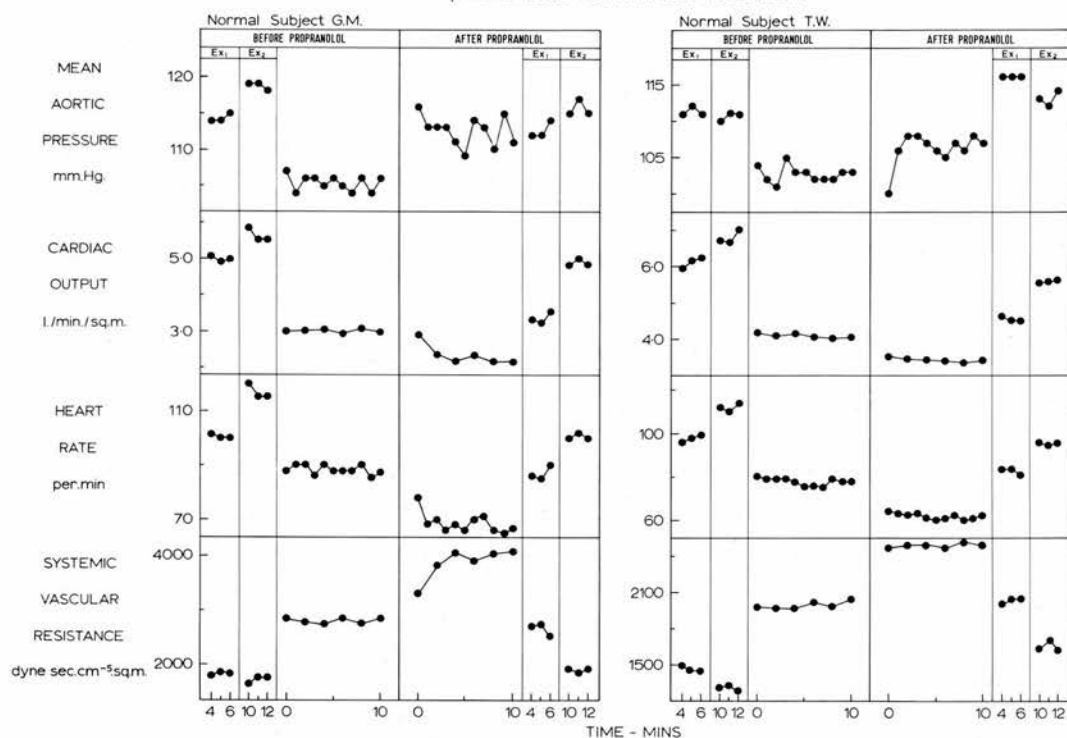


Figure 78

Changes in the systemic circulation during supine leg exercise before and after β -adrenergic block in normal subjects G.M. and T.W.

Heart Rate (Figs. 77 and 78) at rest averaged 77.0 ± 1.04 (S.E.) beats per minute and increased by an average of 25.2% to 96.4 ± 0.66 (S.E.) beats per minute during exercise 1. The heart rate during exercise 2 averaged 114.1 ± 1.18 (S.E. beats per minute, an increase of 48.2% over the mean of resting observations (Table: 53). The difference between the mean values of exercise 1 and 2 was highly significant ($p < 0.001$).

Stroke Volume (Fig. 79) at rest averaged 42.5 ± 0.19 (S.E.) ml./sq.m. and increased in all four subjects during exercise 1 by an average of 22.1% (mean 51.9 ± 0.82 ml./sq.m.) and this was statistically significant ($p < 0.001$). However, during exercise 2 only a little further increase in stroke volume occurred (Table: 53). The difference between the average values of exercise 1 and 2 was only 0.6 ml./sq.m. (1.4%) and this was not statistically significant ($p > 0.5$).

Mean Aortic Pressure (Figs. 77 and 78) did not change significantly in two subjects (W.B. and J.G.) during exercise 1. In the other two subjects (G.M. and T.W.) a small (8.4%) but significant ($p < 0.001$) increase was observed at this time. In three subjects (W.B., G.M. and T.W.) the mean aortic pressure during exercise 2 increased significantly ($p < 0.001$) while in the fourth subject this remained within the range of resting observations (Table: 53). For the group as a whole, the average increases of 4.2% during exercise 1 and 6.6% during exercise 2 were statistically significant ($p > 0.01$ and < 0.001) respectively. The difference between the mean values of exercise 1 and 2 (2.5 mm.Hg) was also statistically significant ($p < 0.05$).

Systemic Vascular Resistance (Figs. 77 and 78) decreased significantly in all subjects during exercise 1 by an average of 34.1%

CHANGES IN STROKE VOLUME DURING SUPINE LEG EXERCISE BEFORE AND AFTER
 β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

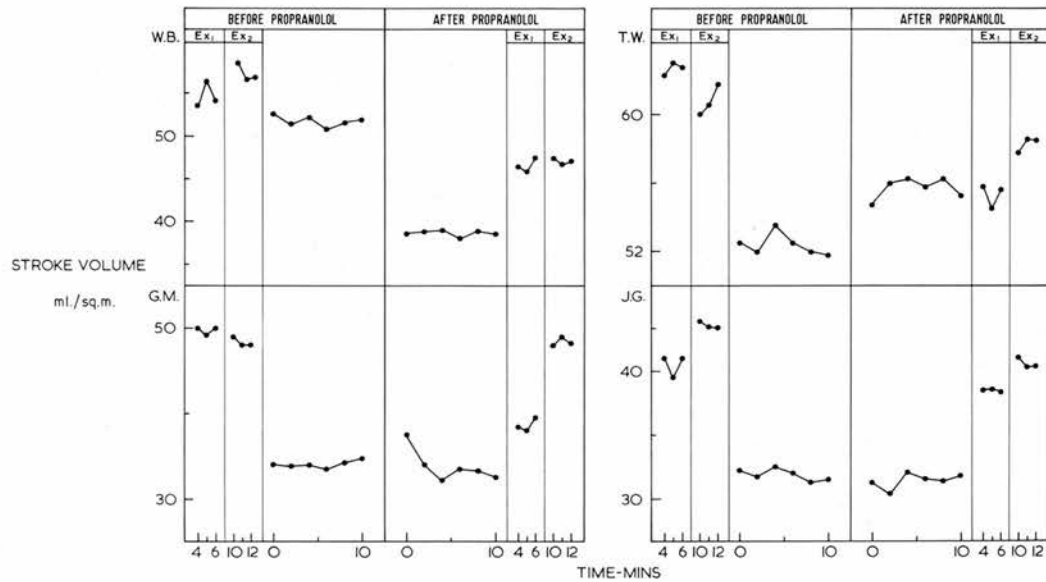


Figure 79

Changes in stroke volume during supine leg exercise before and after β -adrenergic block in 4 normal subjects.

($p < 0.001$). During exercise 2, a further decrease in systemic vascular resistance occurred in all subjects (Table:53). The difference between the mean values of exercise 1 and 2 (12.8%) was highly significant ($p < 0.001$).

Mean Pulmonary Artery Pressure (Figs. 80 and 81) increased in all subjects during exercise 1 but only a small further increase was observed during exercise 2. The mean of the resting observations was 12.8 ± 0.32 (S.E.) mm.Hg and the corresponding figures during exercise 1 and 2 were 18.3 ± 0.33 (S.E.) and 19.9 ± 0.24 (S.E.) mm.Hg. The average percentage increases during the two exercise periods were 43.0 and 55.3 (Table: 54). The difference between the mean values of exercise 1 and 2 (1.6 mm.Hg; 8.7%) was significant ($p < 0.05$).

Mean Pulmonary Wedge Pressure (Figs. 80 and 81) increased in all subjects from a resting average of 5.2 ± 0.25 (S.E.) mm.Hg to 10.1 ± 0.24 (S.E.) and 11.3 ± 0.29 (S.E.) mm.Hg during exercise 1 and 2 respectively (Table: 54). Both the increase during exercise 1 and the difference between the mean values of exercise 1 and 2 (1.2 mm.Hg ; 11.9%) were found to be statistically significant ($p < 0.001$ and < 0.05 respectively).

Pulmonary Vascular Resistance (Figs. 80 and 81) decreased in all four subjects during exercise 1 by an average of 27.5%. During exercise 2 a further decrease was observed in three of the four subjects while a small increase was noted in the fourth subject, (G.M.). However, for the whole group the pulmonary vascular resistance decreased by 38.3% during exercise 2 as compared with the average of resting observations (Table: 54). The difference between the mean values of exercise 1 and 2 (15.0%) was statistically significant ($p < 0.02$).

Cardiopulmonary Blood Volume (Figs. 80 and 81) averaged 392 ± 3 (S.E.) ml./sq.m. at rest and increased significantly ($p < 0.01$) during

CHANGES IN THE PULMONARY CIRCULATION DURING SUPINE LEG EXERCISE BEFORE AND AFTER β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

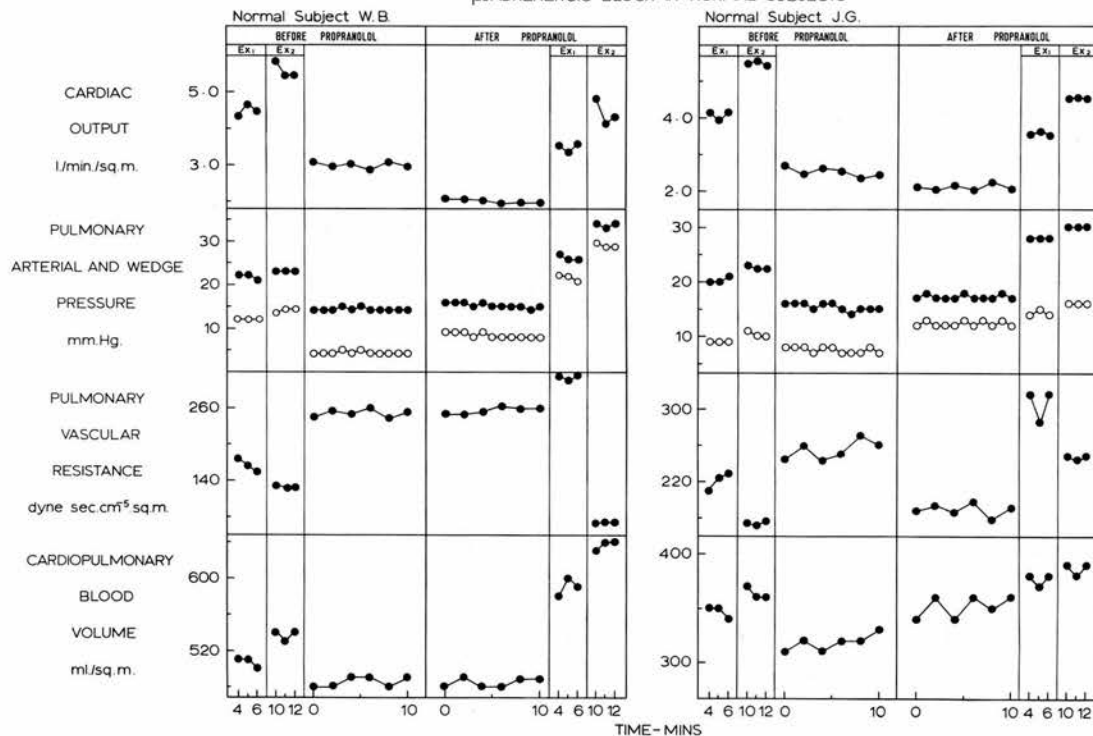


Figure 80

Changes in the pulmonary circulation during supine leg exercise before and after β -adrenergic block in normal subjects W.B. and J.G. Second block from top: filled circles indicate pulmonary artery pressure, open circles indicate pulmonary wedge pressure.

CHANGES IN THE PULMONARY CIRCULATION DURING SUPINE LEG EXERCISE BEFORE AND AFTER β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

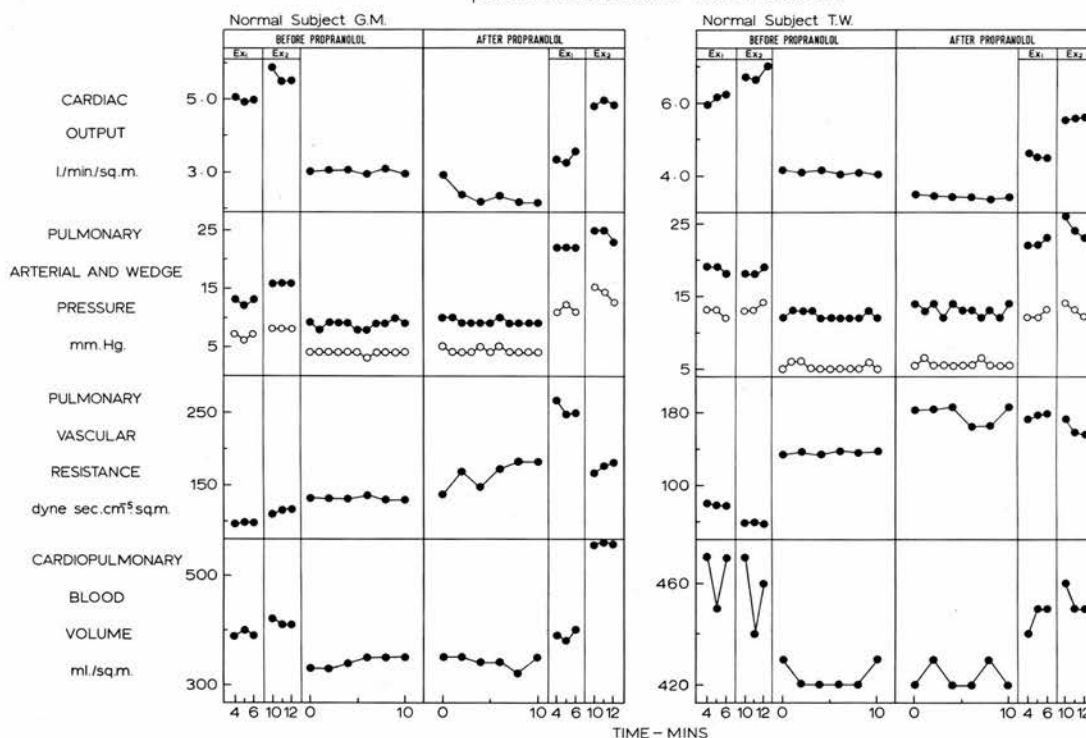


Figure 81

Changes in the pulmonary circulation during supine leg exercise before and after β -adrenergic block in normal subjects G.M. and T.W. Second block from top: filled circles indicate pulmonary artery pressure, open circles indicate pulmonary wedge pressure.

exercise 1 and 2 by 9.2% and 12.8% respectively (Table: 54). However, the difference between the mean values of exercise 1 and 2 (14 ml./sq.m. was not statistically significant ($p > 0.1$).

Mean Right Atrial Pressure (Fig. 82) averaged 2.5 ± 0.12 (S.E.) mm.Hg at rest. Variable changes in individual subjects were observed during exercise 1 and 2 (Table: 54) but the respective mean values of 3.1 ± 0.17 (S.E.) and 2.6 ± 0.37 (S.E.) were not significantly different from the mean of the resting observations ($p > 0.05$ and > 0.8 respectively).

Mean Systolic Ejection Pressure (Table: 55) increased in all four subjects during exercise 1 by an average of 3.6% and a further small increase was observed during exercise 2. Both the average increase during exercise 1 and the difference between the mean values of exercise 1 and 2 were statistically significant ($p < 0.01$).

Left Ventricular Stroke Work (Figs. 83 and 84) averaged 64.5 ± 0.49 (S.E.) g.m./sq.m. during rest and increased by 21.6% and 27.9% during exercise 1 and 2 respectively (Table: 55). The difference between the average values of exercise 1 and 2 (5.2%) was statistically significant ($p < 0.05$).

Duration of Systole (Figs. 83 and 84) varied inversely with the changes in heart rate. The average value of 0.280 ± 0.002 (S.E.) sec. during exercise 1 was not significantly different ($p > 0.05$) from the control mean of 0.286 ± 0.001 (S.E.) sec., but the further decrease to 0.258 ± 0.002 (S.E.) sec. during exercise 2 was a highly significant change ($p < 0.001$).

Mean Stroke Power (Fig. 85) increased by 24.0% and 42.2% during exercise 1 and 2 respectively (Table: 55). Both changes were highly significant ($p < 0.001$) and the difference between the mean values of

CHANGES IN RIGHT ATRIAL PRESSURE DURING SUPINE LEG EXERCISE BEFORE AND AFTER
 β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

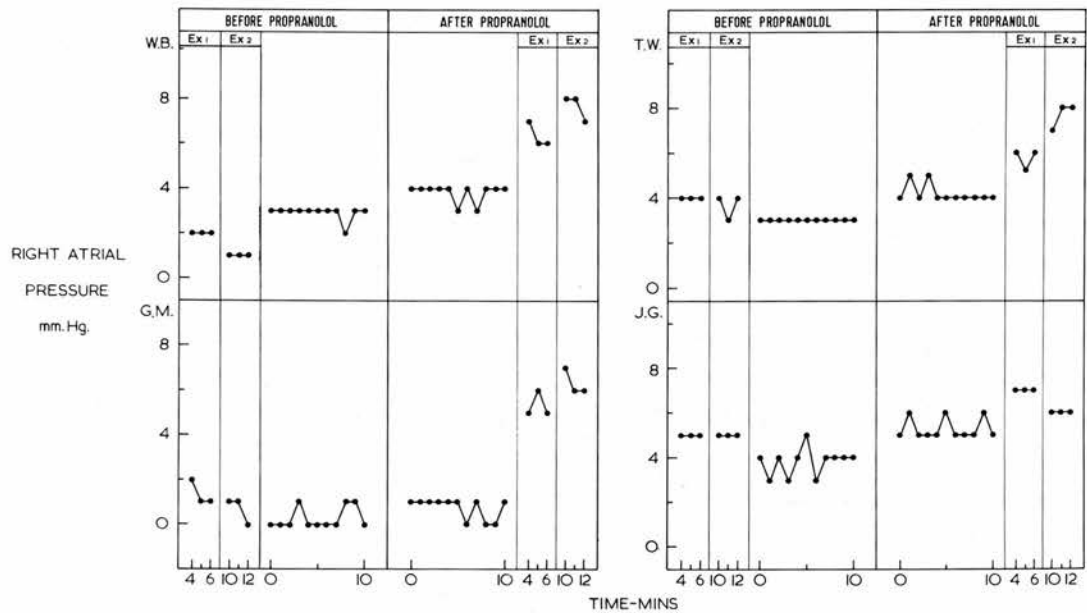


Figure 82

Changes in right atrial pressure during supine leg exercise before and after β -adrenergic block in 4 normal subjects.

CHANGES IN LEFT VENTRICULAR PERFORMANCE DURING SUPINE LEG EXERCISE BEFORE AND AFTER
 β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

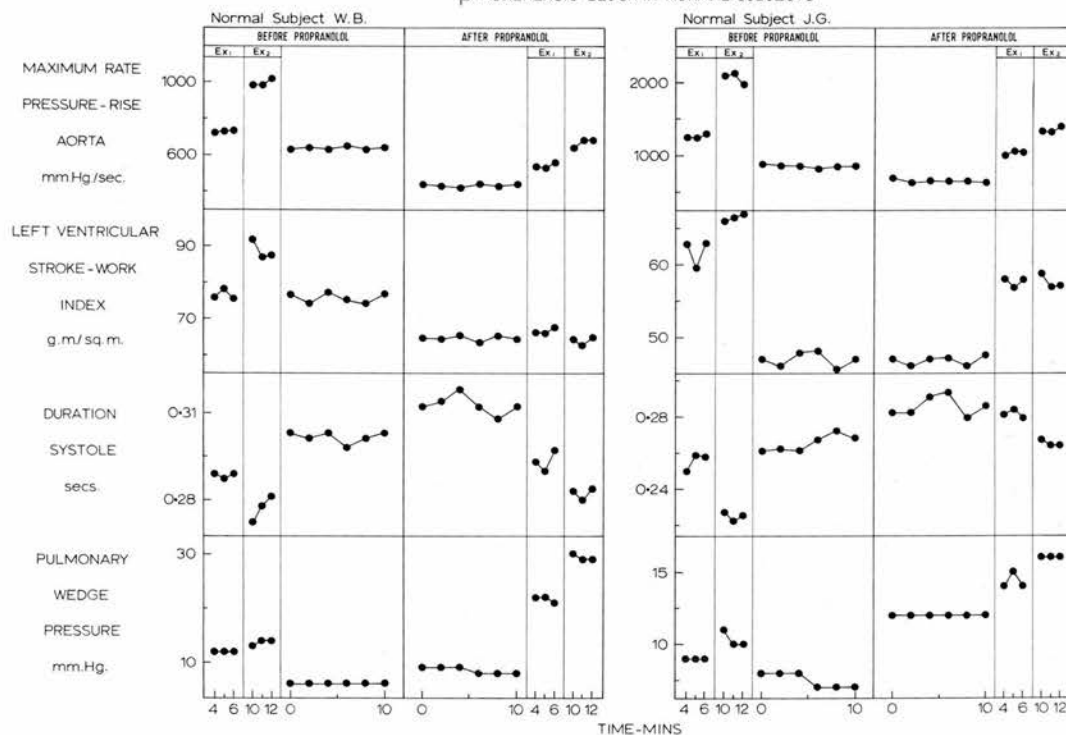


Figure 83

Changes in left ventricular performance during supine leg exercise before and after β -adrenergic block in normal subjects W.B. and J.G.

CHANGES IN LEFT VENTRICULAR PERFORMANCE DURING SUPINE LEG EXERCISE BEFORE AND AFTER
 β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

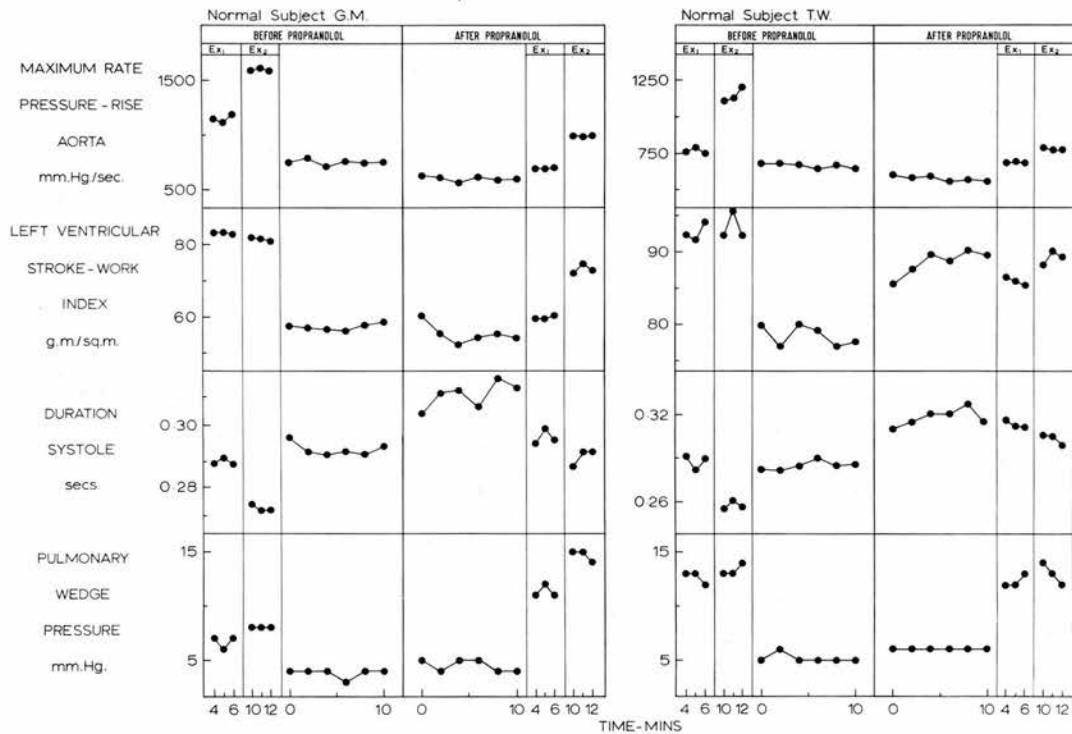


Figure 84

Changes in left ventricular performance during supine leg exercise before and after β -adrenergic block in normal subjects G.M. and T.W.

CHANGES IN MEAN STROKE POWER INDEX DURING SUPINE LEG EXERCISE BEFORE AND AFTER
 β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

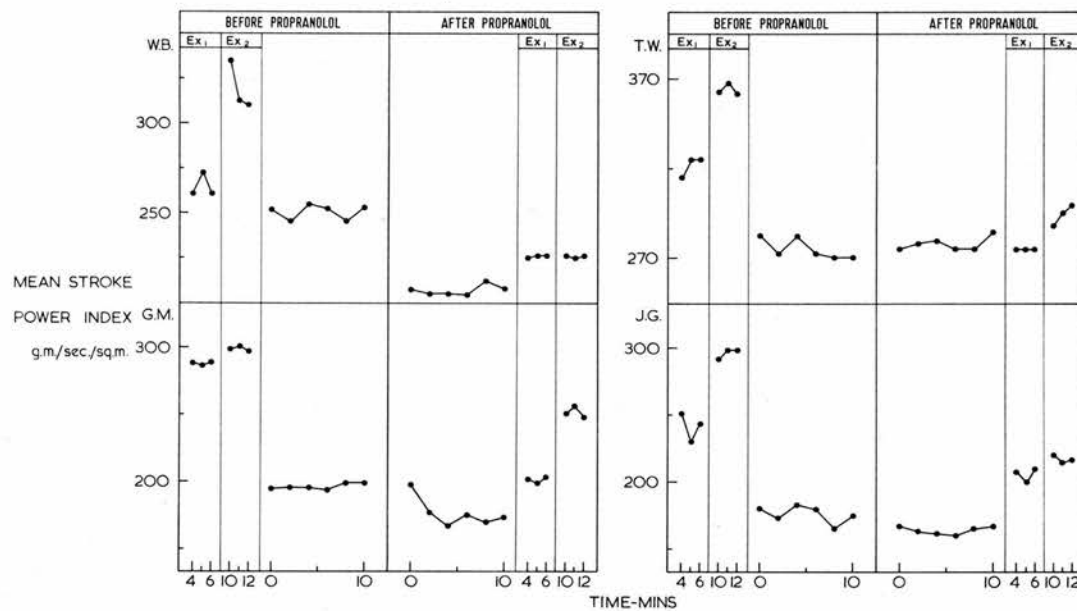


Figure 85

Changes in mean stroke power index during supine leg exercise before and after β -adrenergic block in 4 normal subjects.

exercise 1 and 2 was also significant ($p < 0.01$).

Mean Ejection Flow Index (Fig. 86) also increased by 25.0% and 37.2% during exercise 1 and 2 respectively, and the average value during exercise 2 was significantly greater ($p < 0.01$) than the average value during exercise 1 (Table: 55).

Maximum Rate of Pressure Rise in Aorta (Figs. 83 and 84) showed an average increase of 34.6% and 99.0% during exercise 1 and 2 respectively. The average resting value was 726 ± 7 (S.E.) mm.Hg/sec. and the average values during the two exercise periods were 977 ± 12 (S.E.) and 1445 ± 28 (S.E.) mm.Hg/sec. respectively (Table: 55). Both the increase during exercise 1 and the additional increase from exercise 1 to 2 were statistically significant ($p < 0.001$).

Left Ventricular Minute Work (Figs. 87 and 88) at rest averaged 4.901 ± 0.492 (S.E.) kg.m./min./sq.m. and increased during exercise. The average values of 7.559 ± 0.793 (S.E.) and 9.333 ± 1.007 (S.E.) kg.m./min./sq.m. during exercise 1 and 2 represent an increase over the resting values amounting to 54.2% and 90.4% respectively (Table: 56). The difference between the average values of exercise 1 and 2 was highly significant ($p < 0.001$).

Mean Aortic Diastolic Pressure (Figs. 87 and 88) showed variable changes in individual subjects (Table: 56) but the average figures during exercise 1 and 2 were significantly lower than the mean of control observations ($p \leq 0.01$). However, the difference between the mean values of exercise 1 and 2 was not statistically significant ($p > 0.6$).

Duration of Diastole (Figs. 87 and 88) both per stroke and per minute decreased in all subjects. The average decreases in the diastolic cycle length during exercise periods 1 and 2 were 32.0% and 44.4%. The

CHANGES IN MEAN EJECTION FLOW INDEX DURING SUPINE LEG EXERCISE BEFORE AND AFTER β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

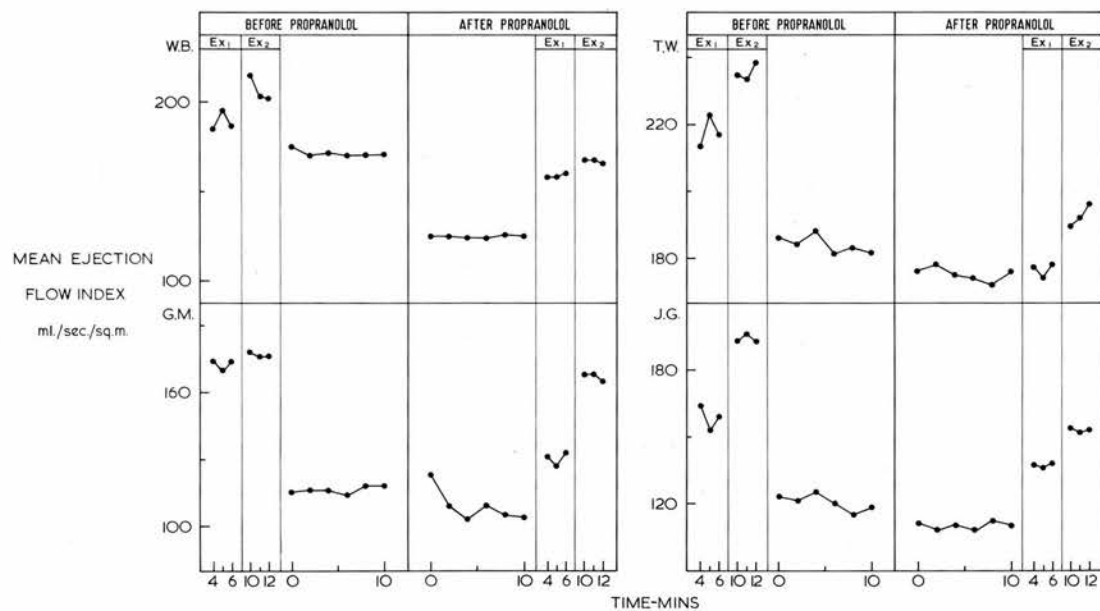


Figure 86

Changes in mean ejection flow index during supine leg exercise before and after β -adrenergic block in 4 normal subjects.

CHANGES IN SOME DETERMINANTS OF CORONARY BLOOD FLOW DURING SUPINE LEG EXERCISE
BEFORE AND AFTER β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

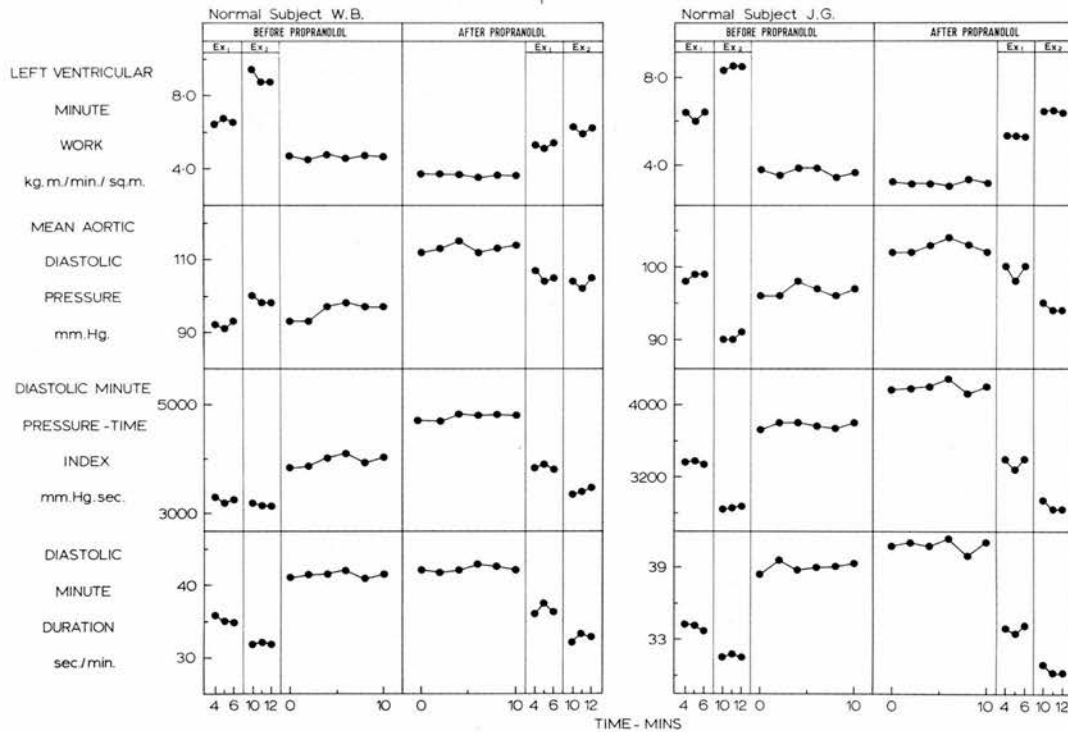


Figure 37

Changes in some determinants of coronary blood flow during supine leg exercise before and after β -adrenergic block in normal subjects W.B. and J.G.

CHANGES IN SOME DETERMINANTS OF CORONARY BLOOD FLOW DURING SUPINE LEG EXERCISE
BEFORE AND AFTER β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

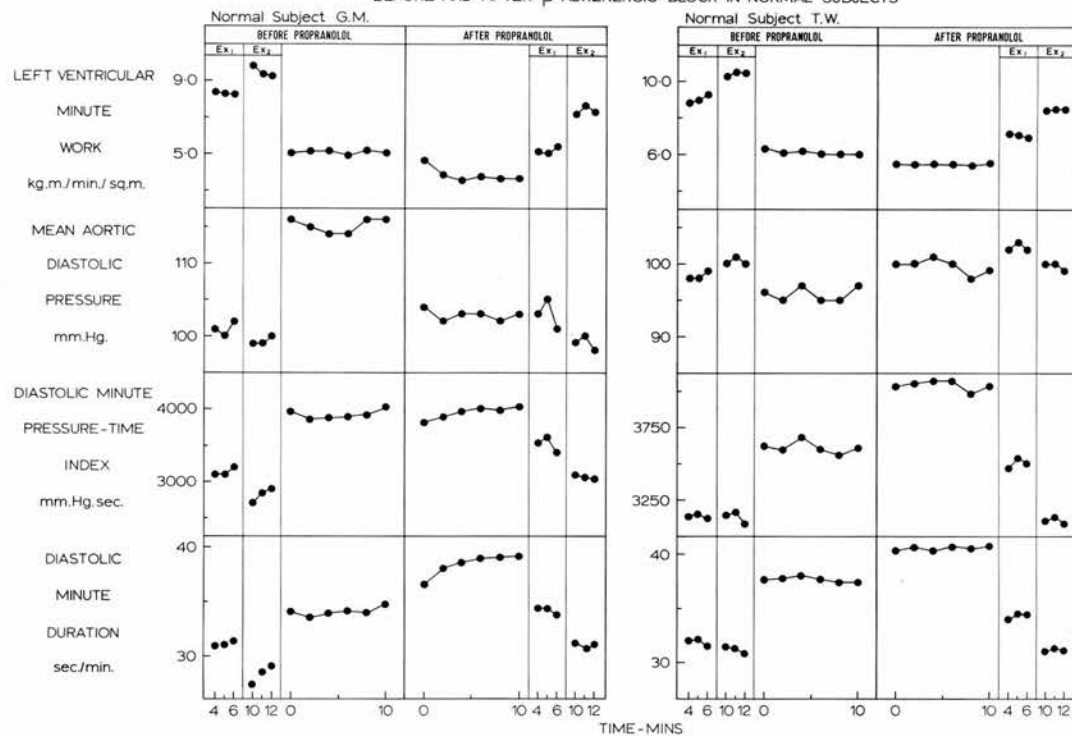


Figure 88

Changes in some determinants of coronary blood flow during supine leg exercise before and after β -adrenergic block in normal subjects G.M. and T.W.

difference between the means of the two exercise periods was statistically significant ($p < 0.001$). Similar changes were also observed in the diastolic minute duration (Table: 56).

Diastolic Minute Pressure-Time Index (Figs. 87 and 88) decreased by 15.7% during exercise 1 and 21.7% during exercise 2 (Table: 56).

The difference between the means of the two exercise periods was significant ($p < 0.01$).

Systolic Minute Pressure-Time Index (Fig. 89) increased in all subjects during exercise. The average increase during exercise 1 was 21.9% and during exercise 2 the corresponding figure was 37.0% (Table: 56). The differences between the average values of exercise 1 and 2 was also significant ($p < 0.01$).

B. Haemodynamic changes at rest following β -adrenergic block:

The statistical significance of the difference between the group means of each variable was assessed by the "Student's" t test performed on the difference between the pairs of mean observations in individual subjects, obtained before and after the administration of propranolol. All changes and percentage figures given are relative to the averages of the "pre-drug" resting observations.

Oxygen Uptake (Fig. 76) at rest before and after β -adrenergic block averaged 139 ± 0.7 (S.E.) and 132 ± 1.3 (S.E.) ml./min./sq.m. respectively and the difference between these values was not statistically significant ($p > 0.8$). However in one subject (W.B.) the oxygen uptake decreased from 155 ± 1.6 (S.E.) ml./min./sq.m. to 124 ± 1.8 (S.E.) ml./min./sq.m. after administration of propranolol and this decrease of 20% was statistically significant ($p < 0.001$). On the other hand the A-V oxygen content difference increased in all subjects after β -adrenergic block by an average of 21.6%

(Table: 53) which was found to be a significant change ($p < 0.01$).

Cardiac Output (Figs. 77 and 78) decreased in all subjects after the administration of propranolol by amounts ranging between 340 (13.5%) and 990 ml./min./sq.m. (31.0%) (Table: 53). The average decrease of 680 ml./min./sq.m. (21.2%) was highly significant ($p < 0.02$).

Heart Rate (Figs. 77 and 78) also decreased significantly ($p < 0.05$) in all subjects, by an average of 13.3 beats per min. (average 17.3%; range 9.3% to 22.0%) (Table: 53).

Stroke Volume (Fig. 79) decreased in one (W.B.) and increased in another (T.W.) subject while no significant changes occurred in the remaining two subjects (Table: 53). For the group the average decrease of 6.3% was not statistically significant ($p > 0.5$).

Mean Aortic Pressure (Figs. 77 and 78) increased in all four subjects by amounts varying between 4.1% and 22.4% (Table: 53). However, the average increase of 9.7% was not statistically significant ($p > 0.05$).

Systemic Vascular Resistance (Figs. 77 and 78) increased in all four subjects (Table: 53) and the average increase of 40.3% (range 24.6% to 76.7%) was statistically significant ($p < 0.05$).

Mean Pulmonary Artery Pressure (Figs. 80 and 81) also increased in all four subjects. Although the increase in individual patients was relatively small (0.5 to 1.9 mm.Hg) the average increase of 0.9 mm.Hg (7.0%) was found to be significant at the 5% level of probability (Table: 54).

Mean Pulmonary Wedge Pressure (Figs. 80 and 81) increased in all subjects. While the average increase in subjects G.M. and T.W. was relatively small (0.4 and 0.9 mm.Hg) quite marked changes (4.2 and 4.9 mm.Hg) were seen in the other two subjects (W.B. and J.G.). The average

CHANGES IN SYSTOLIC MINUTE PRESSURE - TIME INDEX DURING SUPINE LEG EXERCISE BEFORE AND AFTER β -ADRENERGIC BLOCK IN NORMAL SUBJECTS

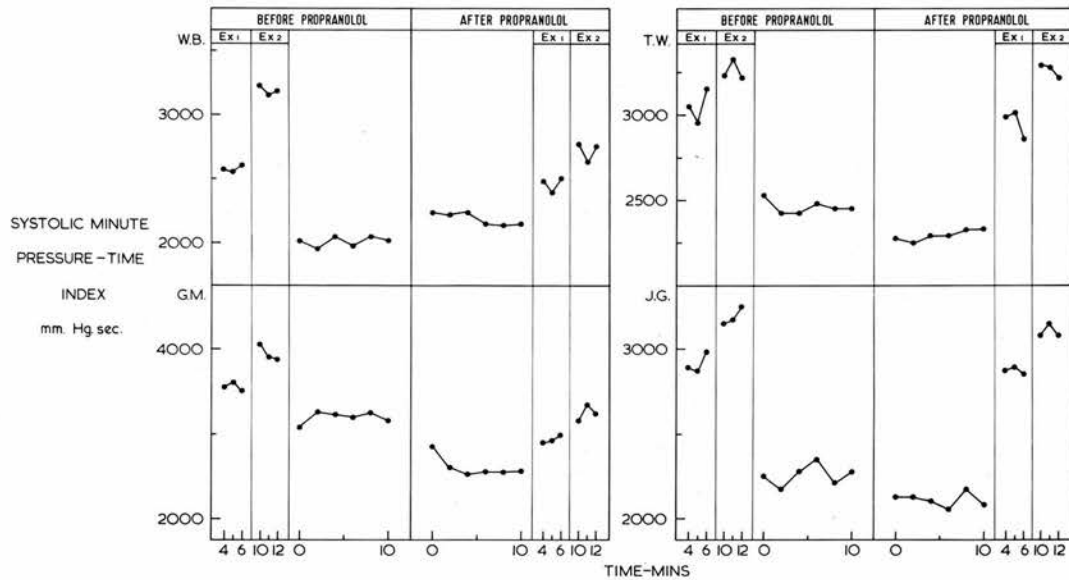


Figure 89

Changes in systolic minute pressure-time index during supine leg exercise before and after β -adrenergic block in 4 normal subjects.

increase of 2.6 mm.Hg (50.0%) in the group was significant ($p < 0.02$) (Table: 54).

Pulmonary Vascular Resistance (Figs. 80 and 81) increased in three subjects (W.B., G.M. and T.W.) while it decreased in the fourth subject (J.G.) (Table: 54). The average change in the group was a small increase of only 2.1% which was not significant ($p > 0.9$).

Cardiopulmonary Blood Volume (Figs. 80 and 81) did not alter in three subjects (W.B., G.M. and T.W.) while this increased (average 10.7%) in the fourth subject (J.G.) (Table: 54). For the group the average increase of 2.0% was not significant ($p > 0.3$).

Mean Right Atrial Pressure (Fig. 82) increased in all four subjects by amounts ranging between 0.4 and 1.5 mm.Hg (Table:54). However, for the group the average increase of 1.0 mm.Hg (40.0%) was not statistically significant ($p > 0.05$).

Mean Systolic Ejection Pressure (Table: 55) increased in three subjects and decreased in the fourth subject but the average increase of 6.5% in the group was not significant ($p > 0.2$).

Left Ventricular Stroke Work (Figs. 83 and 84) showed variable changes, increasing in one subject (T.W.) and decreasing in another two subjects (W.B. and G.M.) while no change was observed in the fourth subject (J.G.) (Table: 55). The group averages before and after the administration of propranolol were not significantly different ($p > 0.8$).

Duration of Systole (Figs. 83 and 84) increased in all subjects but the average increase of 7.3% in the group was not statistically significant ($p > 0.8$)(Table: 55).

Mean Stroke Power Index (Fig. 85) did not change significantly (average decrease of 8.0%; $p > 0.1$) in the group although a marked decrease

of 17.5% was observed in one subject (W.B.) (Table: 55).

Mean Ejection Flow Index (Fig. 86) also decreased in all four subjects (range 4.9% to 27.5%) but the average change in the group (decrease of 12.8%) was not statistically significant ($p > 0.1$) (Table: 55).

Maximum Rate of Pressure Rise in Aorta (Figs. 83 and 84) decreased consistently in all four subjects (Table: 55) and the average decrease of 22.5% in the group was highly significant ($p < 0.001$).

Left Ventricular Minute Work (Figs. 87 and 88) decreased in all four subjects. The average decrease in the group amounting to 17.7% was statistically significant ($p < 0.02$).

Mean Aortic Diastolic Pressure (Figs. 87 and 88) showed variable changes, increasing in three and decreasing in one subject (Table: 56), but the average increase of 3.7% was not significant ($p > 0.5$).

Duration of Diastole (Figs. 87 and 88) increased in all subjects (Table: 56). Both the average increases of 26.2% in diastolic cycle length and 6.6% in diastolic minute duration were significant ($p < 0.02$ and < 0.05 respectively).

Diastolic Minute Pressure-Time Index (Figs. 87 and 88) increased in all subjects (Table: 56) but the average value after the administration of propranolol was not significantly different from the control mean ($p > 0.05$).

Systolic Minute Pressure-Time Index (Fig. 89) decreased in three subjects and increased in one subject (Table: 56) but the average decrease of 7.3% in the group was not statistically significant ($p > 0.3$).

C. Comparison of the haemodynamic changes during supine leg exercise before and after β -adrenergic block:

Essentially similar changes, though differing in magnitude, were

observed during each of the two levels of supine leg exercise both before and after the administration of propranolol. For quantitative comparisons the percentage changes from the means of the corresponding resting averages were obtained for each variable. The significance of the difference between the group average values of these percentage changes were then assessed by the "Student's" t test performed on the differences between the individual pairs of percentage figures thus obtained. The test was performed separately for the percentage changes during each of the two levels of exercise. The results thus obtained are summarised in Tables 53 to 56 and briefly described here. The percentage figures refer to changes from the means of the corresponding resting periods unless otherwise stated.

Oxygen Uptake (Figs. 76 and 90) increased by an average of 165.9% and 295.5% during exercise 1 and 2 respectively (Table: 53). The actual level of oxygen uptake (average values) during exercise 1 was 352 ± 3.9 (S.E.) and 351 ± 3.5 (S.E.) ml./min./sq.m. before and after the administration of propranolol, and the corresponding figures during exercise 2 were 534 ± 6.0 (S.E.) and 522 ± 5.2 (S.E.) ml./min./sq.m. respectively. The differences between the average values of oxygen uptake during the corresponding levels of exercise before and after the administration of propranolol were not statistically significant, (exercise 1: $p > 0.8$; and exercise 2: $p > 0.3$). Likewise the percentage increases during either level of exercise before and after β -sympathetic block were not significantly different (Fig. 90).

The percentage increases in A-V oxygen content differences at either level of exercise after the administration of propranolol were not significantly different from the similar changes during the control period

AVERAGED PERCENTAGE CHANGES DURING EACH OF TWO LEVELS OF SUPINE
LEG EXERCISE BEFORE AND AFTER β -ADRENERGIC BLOCK.

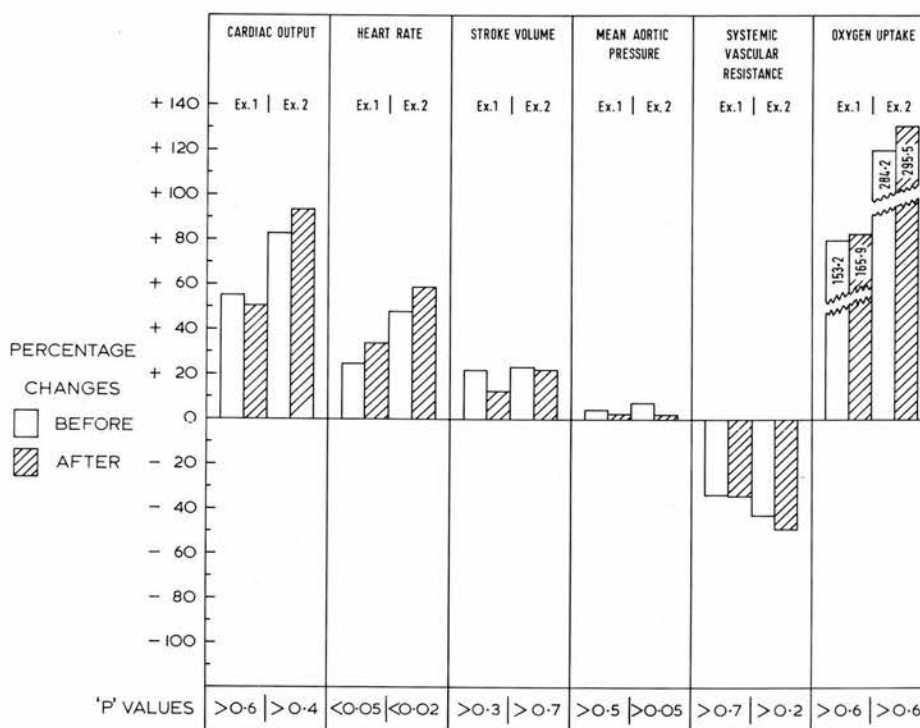


Figure 90

Average percentage changes in cardiac output, heart rate, stroke volume, mean aortic pressure, systemic vascular resistance and oxygen uptake during each of 2 levels of supine leg exercise before and after β -adrenergic block.

(exercise 1: $p > 0.2$; and exercise 2: $p > 0.5$).

Cardiac Output (Figs. 77, 78 and 90) increased to an average of 3.80 ± 0.063 (S.E.) and 4.88 ± 0.045 (S.E.) l./min./sq.m. during exercise 1 and 2 respectively (Table: 53). However, the percentage increases of 50.2% and 92.9% (Fig. 90) from the average of resting measurements were not significantly different from the corresponding figures during the control period ($p > 0.6$ and > 0.4 respectively).

Heart Rate (Figs. 77, 78 and 90) increased to an average of 85.4 ± 1.00 (S.E.) and 101 ± 0.65 (S.E.) beats per min. during exercise 1 and 2 respectively (Table: 53). The percentage increases in heart rate during exercise 1 and 2 from the mean of the resting observations were significantly ($p < 0.05$ and < 0.02 respectively) greater after the administration of propranolol as compared with the similar changes during the control observations.

Stroke Volume (Figs. 79 and 90) after β -sympathetic block increased significantly during exercise 1 ($p < 0.01$) and, unlike the control observations a further small but significant increase (8.7%) was observed during exercise 2 ($p < 0.001$). The percentage increase in stroke volume at either exercise level after β -adrenergic block was not significantly different from the corresponding figures of the control period (Table: 53 and Fig. 90).

Mean Aortic Pressure (Figs. 77, 78 and 90) increased in one subject (T.W.) while no significant changes compared with the average resting values were seen in the other three subjects. For the group the average increases of 2.2% and 1.8% during exercise 1 and 2 (Table: 53) were not significantly different from the corresponding figures obtained during the control period ($p > 0.5$ and > 0.5) (Fig. 90).

Systemic Vascular Resistance (Figs. 77, 78 and 90) decreased significantly during exercise 1 and a further significant decrease (22.6%) was observed during exercise 2 ($p < 0.001$). However the differences between the percentage changes, at either level of exercise, before and after β -adrenergic block were not statistically significant ($p > 0.7$ and $p > 0.2$) (Table: 53 and Fig. 90).

Mean Pulmonary Artery Pressure (Figs. 80, 81 and 91) increased during exercise 1 (average 24.7 ± 0.24 mm.Hg = 80.3%) and a further significant ($p < 0.01$) increase from these figures occurred during exercise 2 (average 30.0 ± 0.58 = 119.0%). However the percentage increase from the mean of the resting observations during exercise 1 was not significantly different ($p > 0.1$) from the corresponding figure obtained during the control period, while during exercise 2 these differences achieved significance at a probability level of 5% (Table: 54 and Fig. 91).

Mean Pulmonary Wedge Pressure (Figs. 80, 81 and 91) also increased during exercise 1 and a further significant increase ($p < 0.01$) occurred during exercise 2. However the percentage increases at either level of exercise before and after the administration of propranolol were not significantly different (exercise 1: $p > 0.8$; and exercise 2: $p > 0.5$) (Table: 54 and Fig. 91).

Pulmonary Vascular Resistance (Figs. 80, 81 and 91) increased in three subjects during exercise 1 while no significant change was observed in the fourth subject (T.W.). However, the average increase of 33.5% during exercise 1 was statistically significant ($p < 0.01$). The difference between the percentage changes during exercise 1 before and after β -adrenergic block was also highly significant ($p < 0.01$). During exercise 2 the pulmonary vascular resistance decreased relative to the average

AVERAGED PERCENTAGE CHANGES DURING EACH OF TWO LEVELS OF SUPINE
LEG EXERCISE BEFORE AND AFTER β -ADRENERGIC BLOCK.

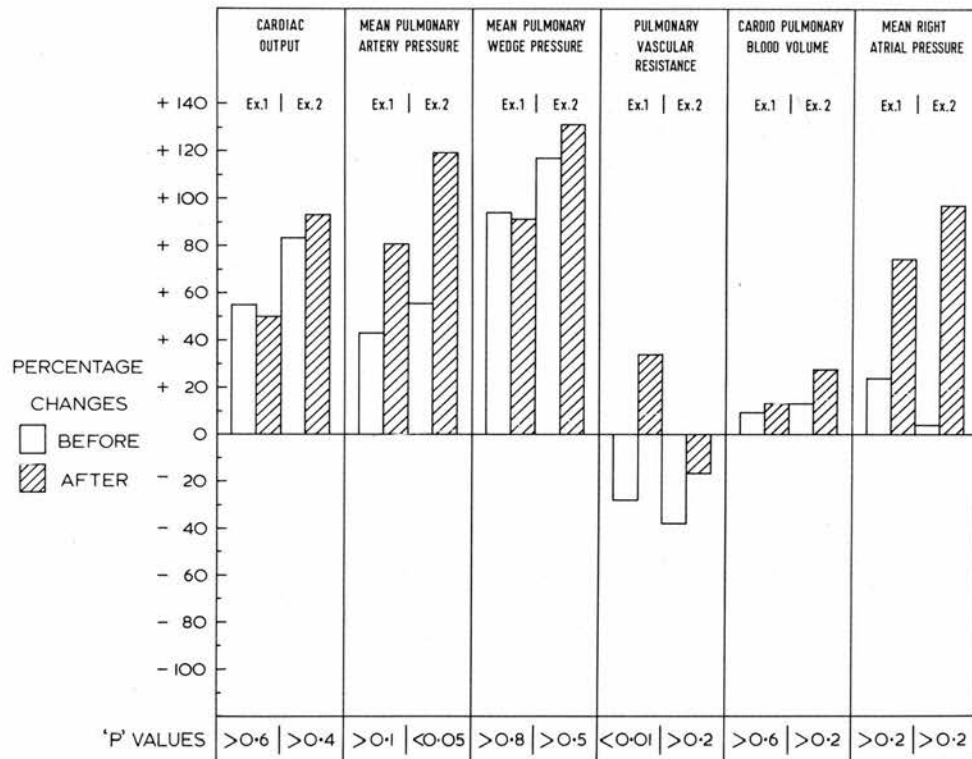


Figure 91

Average percentage changes in cardiac output, mean pulmonary artery pressure, mean pulmonary wedge pressure, pulmonary vascular resistance, cardiopulmonary blood volume and mean right atrial pressure during each of 2 levels of supine leg exercise before and after β -adrenergic block.

values observed during exercise 1. In two subjects (J.G. and G.H.) the pulmonary vascular resistance during exercise 2 was still higher than the mean of the control observations while in the other two subjects (W.B. and T.W.) it even decreased below this level. The average change during exercise 2 was a significant decrease of 16.7% ($p < 0.01$) relative to the resting observations. The difference between the percentage decreases during exercise 2 from the corresponding resting observations before and after the administration of propranolol was not statistically significant ($p > 0.2$) (Table: 54 and Fig. 91).

Cardiopulmonary Blood Volume (Figs. 80, 81 and 91) increased during exercise 1 and 2 to 451 ± 5 (S.E.) and 510 ± 3 (S.E.) ml./sq.m. respectively. Both the increase during exercise 1 relative to the average of resting observations and the difference between the mean values of exercise 1 and 2 were statistically significant ($p < 0.001$). However the differences between the percentage increases during exercise 1 and 2 before and after β -adrenergic block were not significant (exercise 1: $p > 0.6$; and exercise 2: $p > 0.2$) (Table: 54 and Fig. 91).

Mean Right Atrial Pressure (Figs. 82 and 91) increased significantly in all subjects during exercise 1, but the small further increase (0.8 mm.Hg) during exercise 2 was not statistically significant ($p > 0.2$). The differences between the percentage increases from the resting means at either level of exercise before and after β -adrenergic block were not statistically significant ($p > 0.2$) (Table: 54 and Fig. 91.).

Mean Systolic Ejection Pressure (Table: 55) showed variable changes during exercise after β -adrenergic block and for the group the average values of exercise 1 and 2 were not significantly different from the mean of resting observations (exercise 1: $p > 0.5$; and exercise 2: $p > 0.9$).

Likewise the differences between the percentage changes at either level of exercise before and after the administration of propranolol were not statistically significant ($p > 0.05$).

Left Ventricular Stroke Work (Figs. 83, 84 and 92) changed but little in two subjects (W.B. and T.W.) while this increased in the other two subjects (J.G. and G.M.). For the group the average increases of 6.0% and 11.3% during exercise 1 and 2 respectively were statistically significant ($p < 0.01$). The percentage increases from the resting mean values during both exercise 1 and 2 were significantly lower than the corresponding changes during the control period (exercise 1: $p < 0.05$; and exercise 2: $p < 0.001$) (Table: 55 and Fig. 92).

Duration of Systole (Figs. 83, 84 and 92) varied inversely with the changes in heart rate. The percentage decreases during exercise 1 and 2 were 3.6 and 7.2 respectively but these figures were not significantly different ($p > 0.2$) from the corresponding figures during the control period (Table:55 and Fig. 92).

Mean Stroke Power Index (Figs. 85 and 92) increased in all subjects, the average rise amounting to 9.7% and 19.8% during exercise 1 and 2 respectively. While the former percentage increase was not significantly different from the corresponding figure obtained during the control period, the small increase of 19.8% during exercise 2 was significantly lower ($p < 0.05$) than the corresponding figure of 42.2% observed during the control period (Fig. 92).

Mean Ejection Flow Index (Figs. 86 and 92) increased during exercise 1 and a further significant ($p < 0.01$) increase occurred during exercise 2. However no significant difference could be shown for the percentage increases at either level of exercise before and after the

AVERAGED PERCENTAGE CHANGES DURING EACH OF TWO LEVELS OF SUPINE
LEG EXERCISE BEFORE AND AFTER β -ADRENERGIC BLOCK.

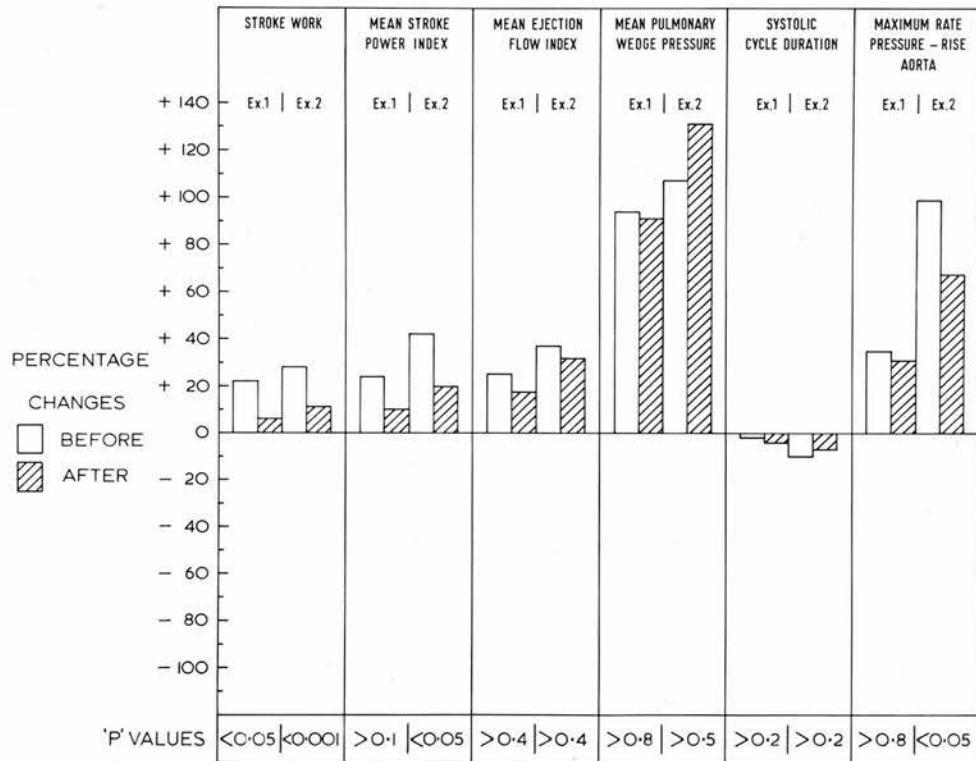


Figure 92

Average percentage changes in stroke work, mean stroke power index, mean ejection flow index, mean pulmonary wedge pressure, systolic cycle duration and maximum rate pressure-rise in aorta during each of 2 levels of supine leg exercise before and after β -adrenergic block.

administration of propranolol ($p > 0.4$) (Table: 55 and Fig. 92).

Maximum Rate of Pressure Rise in Aorta (Figs. 83, 84 and 92)

increased in all subjects during exercise and the average value during exercise 2 was significantly ($p < 0.001$) higher than that during exercise 1. The difference between the percentage increases during exercise 1 before and after β -adrenergic block was not significant ($p > 0.8$) but during exercise 2 this difference was statistically significant ($p < 0.05$) (Table : 55 and Fig. 92).

Left Ventricular Minute Work (Figs. 87, 88 and 93) increased

in all subjects during exercise 1 and a further significant increase ($p < 0.001$) was observed during exercise 2. However the differences between the percentage increases at either level of exercise before and after the administration of propranolol were not significant (Table: 56 and Fig.93).

Mean Aortic Diastolic Pressure (Figs. 87, 88 and 93) did not

change significantly during exercise 1 ($p > 0.05$) while the decrease of 5.2% during exercise 2 achieved statistical significance at a probability level of 1%. However the percentage change in either instance was not significantly different from the corresponding percentage changes during the control period ($p > 0.5$). (Table: 56 and Fig. 93).

Duration of Diastole (Figs. 87, 88 and 93) both per cycle and

per minute decreased in all subjects (Table: 56), and the proportional changes during either level of exercise before and after the administration of propranolol were not significantly different (Table: 56 and Fig. 93).

Diastolic Minute Pressure-Time Index (Figs. 87, 88 and 93) also

decreased in all subjects but again no significant difference could be demonstrated between the percentage changes before and after β -adrenergic block (Table: 56 and Fig. 93).

AVERAGED PERCENTAGE CHANGES DURING EACH OF TWO LEVELS OF SUPINE
LEG EXERCISE BEFORE AND AFTER β -ADRENERGIC BLOCK.

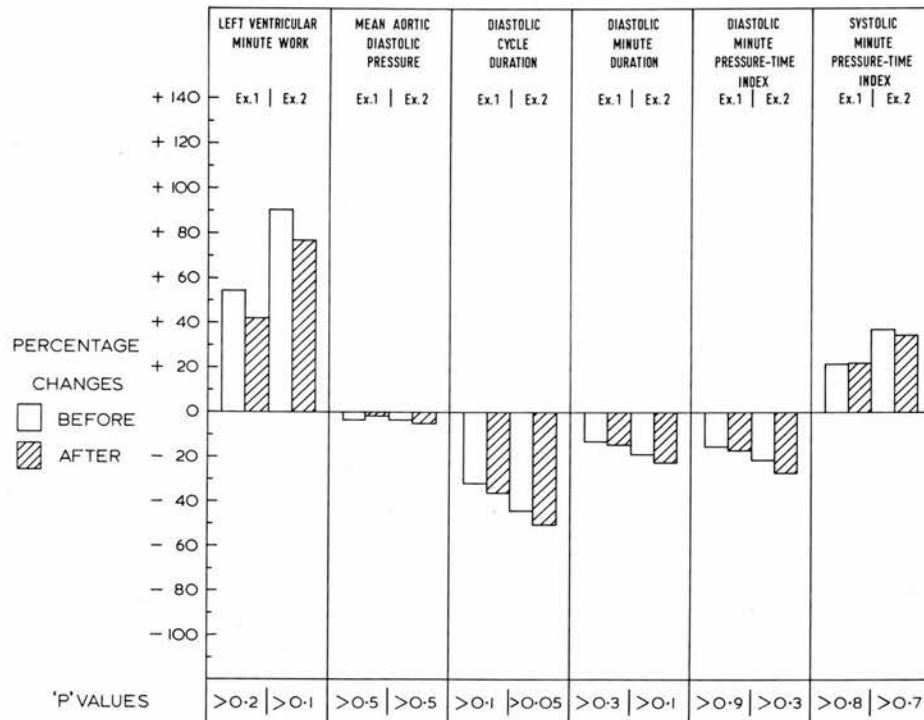


Figure 93

Average percentage changes in left ventricular minute work, mean aortic diastolic pressure, diastolic cycle duration, diastolic minute duration, diastolic minute pressure-time index and systolic minute pressure-time index during each of 2 levels of supine leg exercise before and after β -adrenergic block.

Systolic Minute Pressure-Time Index (Figs. 89 and 93) increased significantly during exercise 1 and again during exercise 2. However, no significant difference was found between the proportional changes in each instance before and after the administration of propranolol (Table:56 and Fig.93).

On further consideration of the data and the results of the comparisons between the magnitude of the various changes before and after β -adrenergic block as detailed above, it was felt that the tests, though perfectly valid, did not provide a complete picture. A further comparison with the help of standard regression analysis was, therefore, undertaken. Only some of the more important variables, namely cardiac output, heart rate, stroke volume, left ventricular minute and stroke work and mean pulmonary wedge pressure, were treated in this way and the results obtained are shown in Fig. 94 and Fig.95.

The oxygen uptake was used in these analyses as the common denominator indicating the level of exercise and the regression lines were calculated using oxygen uptake as the independent variable. Since the aim was to compare only the changes in the response to supine leg exercise before and after β -adrenergic block, the data from each of the four subjects was pooled including both the resting and exercise observations. This was considered justifiable in view of the limited requirements of the test. However, the uneven distribution of the observations about the regression lines (because of small sample size) does not allow confidence intervals to be attached to these lines, and these were not, therefore, calculated.

For each variable the solid line in Figs. 94 and 95 represents the best fit for the observations obtained before the administration of propranolol while the interrupted line is based on the data obtained after the administration of propranolol. Both the slopes and intercepts of the

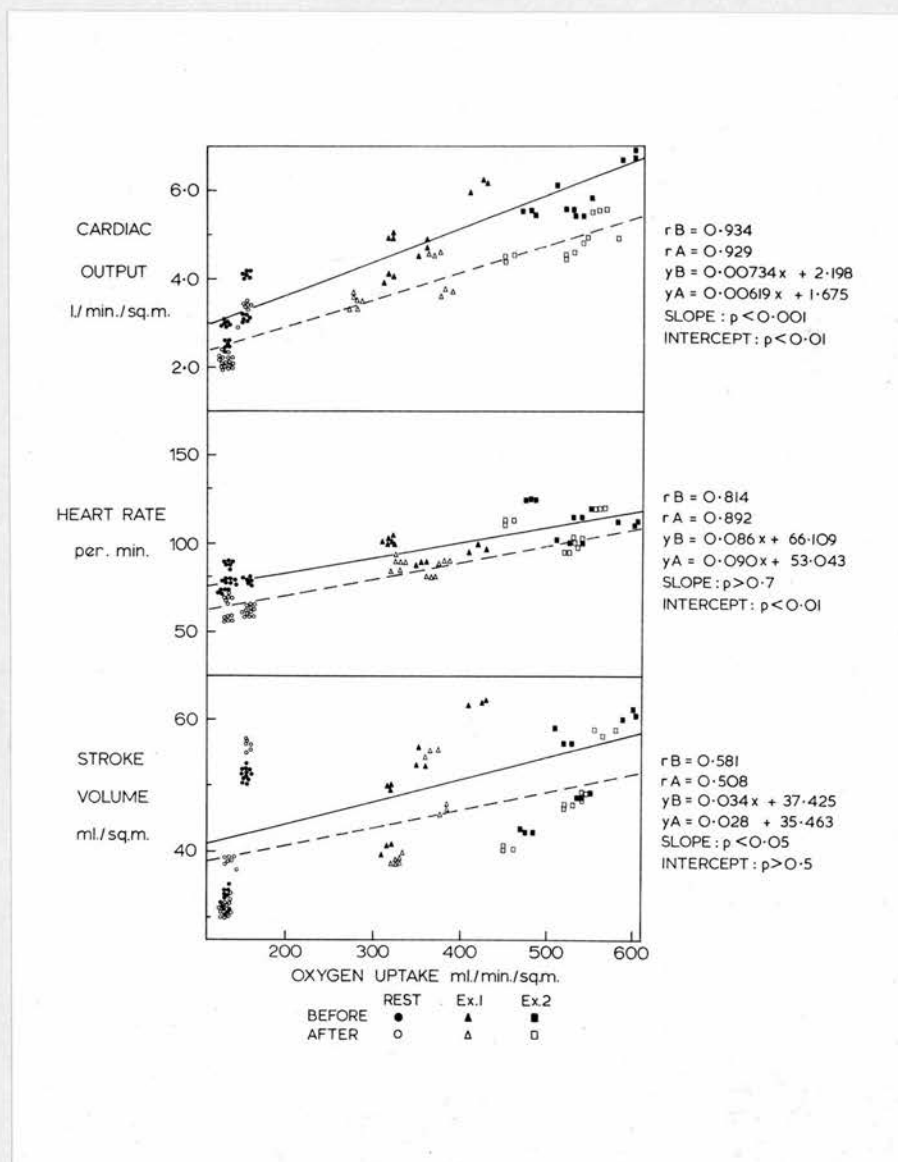


Figure 94

The changes in cardiac output, heart rate and stroke volume during supine leg exercise before and after β -adrenergic block in four normal subjects. Individual observations of each patient have been plotted. Oxygen uptake has been used as the independent variable along the x axis and the regression lines of y on x are shown. The solid and interrupted lines are the best fit for the data obtained before and after β -adrenergic block respectively.
 r = correlation co-efficient.

B = Before

A = After

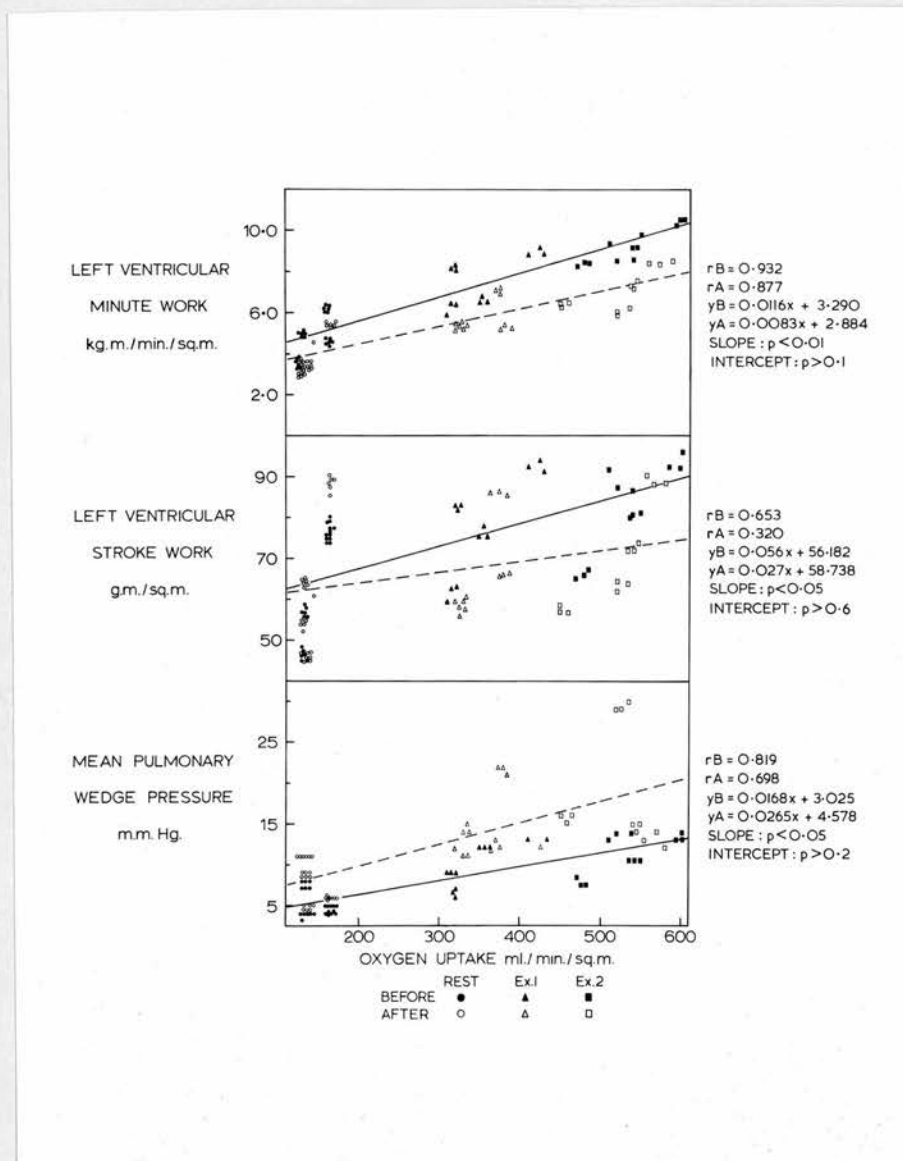


Figure 95

The changes in left ventricular minute work, left ventricular stroke work and mean pulmonary wedge pressure during supine leg exercise before and after β -adrenergic block in four normal subjects. Individual observations of each patient have been plotted. Oxygen uptake has been used as the independent variable along the x axis and the regression lines of y on x are shown. The solid and interrupted lines are the best fit for the data obtained before and after β -adrenergic block respectively. r = correlation co-efficient.

B = Before

A = After

two sets of lines thus obtained for each variable were then compared to assess the significance of the differences, if any.

When the cardiac output response to exercise was examined in this way (Fig. 94) a significant difference in both the slope and intercept of the two lines was found. This suggests that after the administration of propranolol the subjects started at a lower level of cardiac output, and that the increase in cardiac output per unit increase in oxygen uptake was relatively smaller when compared with the changes during the control period. Thus the cardiac output during exercise in the control period increased by an average of 734 ml./min./sq.m. for every increase of 100 ml./min./sq.m. in oxygen uptake. The corresponding rate of increase in the cardiac output after β -adrenergic block was 619 ml./min./sq.m.

Similar significant differences in the slopes of the regression lines were found for the changes in stroke volume, left ventricular minute work, stroke work and mean pulmonary wedge pressure (Figs. 94 and 95). However, for each of these variables the intercepts were not significantly different. Thus following β -adrenergic block the changes in stroke volume, left ventricular minute work and left ventricular stroke work were significantly less marked as compared to similar changes during exercise in the control period. On the other hand, the mean pulmonary wedge pressure increased more rapidly during exercise after the administration of propranolol than during exercise in the control period (Fig. 95).

The slopes of the regression lines for changes in heart rate before and after the administration of propranolol were not significantly different but the difference between the intercepts were significant (Fig. 94). Thus β -adrenergic block did not affect the rate of increase in heart rate during exercise although the subjects started from a significantly lower heart rate after the administration of propranolol.

DISCUSSION

A. Haemodynamic changes during supine leg exercise before β -adrenergic block:

The haemodynamic changes observed during the two levels of supine leg exercise, before the administration of propranolol, were in accord with the results reported by several workers and summarised in the introduction to this Chapter. The salient features of the changes observed in the present study can be summarised as follows:

Changes in the Systemic Circulation: The oxygen uptake increased by about $2\frac{1}{2}$ times of the average resting value during the lighter exercise load (exercise 1) and approximately $4\frac{1}{2}$ times during the heavier level of exercise (exercise 2). Thus the level of exercise in either instance was mild relative to the maximal exercise that most young normal subjects are capable of.

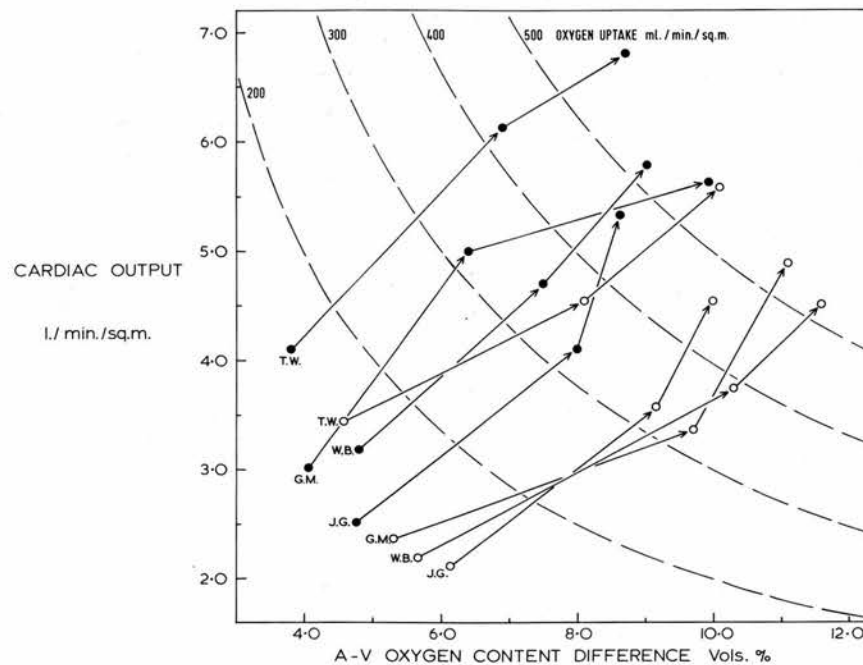
Both the cardiac output and A-V oxygen content difference increased almost linearly with the increase in oxygen uptake (Fig. 96).

The increase in cardiac output was mainly brought about by an increase in heart rate (Fig. 97). The increase in stroke volume, which was most marked in two subjects, during the first level of exercise may well have been a result of the elevation of the lower limbs before the commencement of exercise (Frick and Somer, 1964). Only a small and insignificant further increase in stroke volume was observed during the second level of exercise.

Variable changes in mean aortic pressure were seen during exercise 1 but it increased in three of the four subjects during the heavier exercise load.

The systemic vascular resistance consistently decreased in all four subjects during exercise 1 and a further significant reduction occurred during exercise 2 (Fig. 98).

CHANGES IN CARDIAC OUTPUT, A-V OXYGEN CONTENT DIFFERENCE AND OXYGEN UPTAKE DURING SUPINE LEG EXERCISE BEFORE AND AFTER β -ADRENERGIC BLOCK



CHANGES IN HEART RATE, STROKE VOLUME AND CARDIAC OUTPUT DURING
SUPINE LEG EXERCISE BEFORE AND AFTER β -ADRENERGIC BLOCK

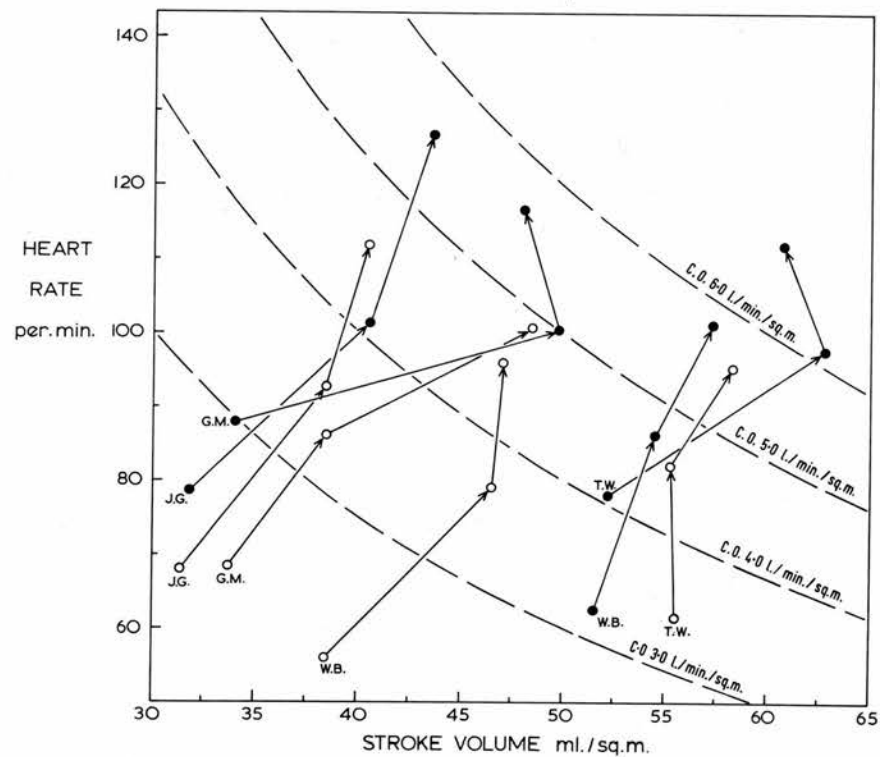


Figure 97

The changes in heart rate, stroke volume and cardiac output during supine leg exercise before and after β -adrenergic block. Only the average values of each period are shown. The arrows indicate the change from rest to Exercise 1 and Exercise 2. Solid circles represent observations before, and open circles observations after β -adrenergic block.

CHANGES IN CARDIAC OUTPUT, SYSTEMIC VASCULAR RESISTANCE AND MEAN AORTIC PRESSURE
DURING SUPINE LEG EXERCISE BEFORE AND AFTER β -ADRENERGIC BLOCK

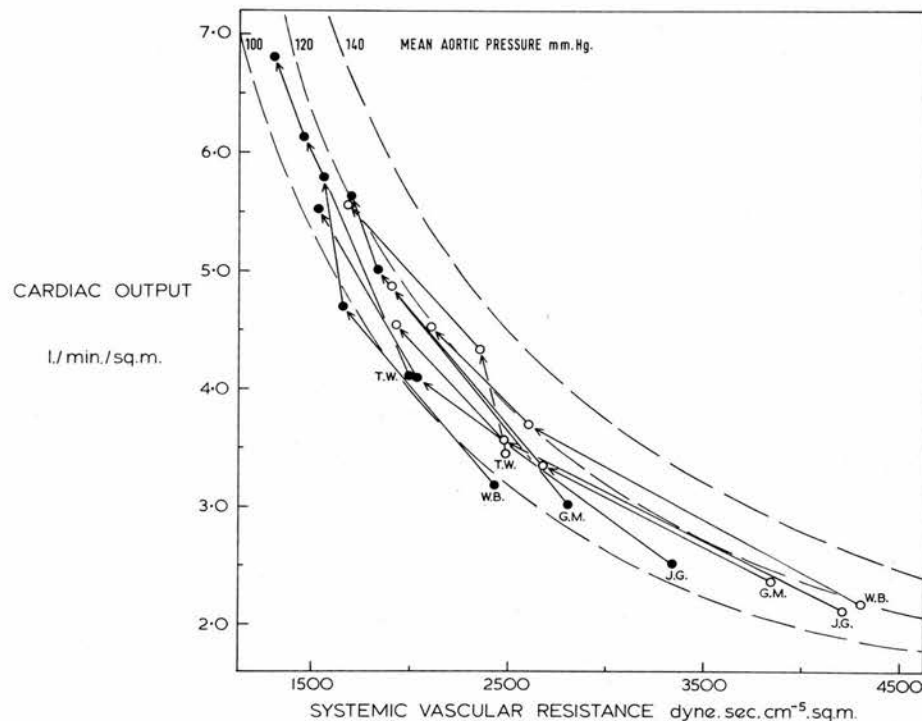


Figure 98

The changes in cardiac output, systemic vascular resistance and mean aortic pressure during supine leg exercise before and after β -adrenergic block. Only the average values of each period are shown. The arrows indicate the change from Rest to Exercise 1 and Exercise 2. Solid circles represent observations before, and open circles observations after β -adrenergic block.

Similar changes in the systemic circulation during supine leg exercise have been observed by most workers (Dexter et al, 1951; Donald et al, 1955; Freedman et al, 1955; and Bevegård et al, 1963).

Changes in the Pulmonary Circulation: Both the mean pulmonary artery and wedge pressures increased during exercise 1 and a further but much smaller, though significant, increase in both pressures was observed during exercise 2.

No secondary fall in the mean pulmonary artery pressure was observed in the present study. However, since each level of exercise was maintained for only 6 minutes it is not possible to comment upon the findings of Sancetta and Rakita (1957) who reported a secondary fall in this pressure when exercise was maintained at the same level for longer than 5 to 6 minutes.

The pulmonary vascular resistance decreased in all subjects during exercise 1 and a further decrease occurred during exercise 2 in three of the four subjects.

The cardiopulmonary blood volume increased in all subjects during exercise 1, but the additional increase during exercise 2 was not found to be statistically significant. It should however be pointed out that the actual volume estimated by the technique used in the present study includes the volume of the left ventricle and the left atrium. Since the end-diastolic volume of the left ventricle decreases during exercise (Braunwald et al, 1963; Gorlin et al, 1965; and Sonnenblick et al, 1965) the actual increase in the pulmonary blood volume was probably much greater than that indicated by the results of the present study. Both Mitchell et al (1958b) and Braunwald and Kelly (1960) were using a similar technique to that used in the present study, so that even their results probably underestimate the

increase in pulmonary blood volume. Daly et al (1965) have recently confirmed, with the help of a more direct technique, that the pulmonary capillary blood volume increases during both supine and upright exercise.

The precise mechanism of this increase in pulmonary blood volume during exercise is not known but there is strong suggestive evidence indicating a redistribution of the circulating blood volume due mainly to the venoconstriction that occurs during dynamic exercise (Guyton, 1963; and Bevegard and Shepherd, 1965).

The mean right atrial pressure did not show any consistent changes and the average values during the two levels of exercise were not significantly different from the control mean. Variable changes in mean right atrial pressure have also been observed by other workers (Asmussen and Nielsen, 1955; Holmgren, 1956; and Barratt-Boyes and Wood, 1957).

Changes in Left Ventricular Performance: Left ventricular stroke work, mean stroke power index, and mean ejection flow index increased consistently in all subjects.

It has recently been shown that left ventricular stroke work, stroke power, and ejection flow rate decrease with increasing rates at which the human heart is paced (Stein et al, 1966; and Benchimol and Liggett, 1966). Similar changes in these parameters have been reported with increasing pacemaker frequency during both rest and exercise (Stein et al, 1966). In view of these reports the findings from the present study can be interpreted as indicating an increase in myocardial contractility which is not related to changes in heart rate.

Furthermore, as already pointed out, the left ventricular end-diastolic volume frequently decreases during exercise. Thus it would appear that the increase in stroke work, mean stroke power index, and mean ejection flow

index, observed in the present study, occurred in spite of a decrease in end-diastolic fibre length (volume). On the other hand, the increase in mean pulmonary wedge pressure, also observed in the present study, indicates an increase in left ventricular end-diastolic pressure (Chapter III). However, since intrathoracic pressure changes were not taken into account while measuring the mean pulmonary wedge pressure it is not possible to comment upon the changes in the "effective" left ventricular end-diastolic pressure during exercise. Changes in the end-diastolic volume of the ventricle are related to the "effective" end-diastolic pressure and not to the absolute pressure.

The maximum rate of pressure rise in the aorta increased in all subjects during exercise. However, in the absence of information about the precise functional significance of this measurement (Chapter II) no definite conclusions can be drawn from the changes in the maximum rate of pressure rise in the aorta observed in the present study. It has been shown that the maximum rate of pressure rise (dp/dt) in the ventricle increases during exercise (Sonnenblick et al, 1965) and this is interpreted as indicating an increase in myocardial contractility (Siegel et al, 1964).

The left ventricular minute work increased in all subjects during exercise. On the other hand the diastolic minute pressure-time index decreased while the systolic minute pressure-time index increased significantly in all subjects.

Gorlin et al (1965) have demonstrated that the coronary blood flow and myocardial oxygen consumption are augmented during exercise, and that the efficiency of the left ventricle is increased.

No direct measurements of coronary blood flow and/or myocardial oxygen consumption were made in the present study. The increase in the

systolic minute pressure-time index would imply increased myocardial oxygen consumption (Chapter : II).

The decrease in diastolic minute pressure-time index is contrary to the observations of Gorlin et al (1964). These authors found a 13% decrease in the coronary inflow time (duration of diastole) but the diastolic perfusion pressure increased by 12%. With the help of a more direct technique (nitrous oxide dilution) they reported an increase of 22% in the coronary blood flow. A decrease in the coronary vascular resistance is implied in these findings.

There are, at present, five reports in the literature in which the effects of B-adrenergic block on the haemodynamic response to dynamic exercise in man have been studied (Chamberlain and Howard, 1964; Schroder and Werko, 1965; Segel and Bishop, 1965; Epstein et al, 1965; and Sonnenblick et al, 1965). In three of these studies (Chamberlain and Howard, 1964; Schroder and Werko, 1965; and Epstein et al, 1965) exercise was performed either in the upright or sitting postures. Segel and Bishop (1965) studied the changes during both supine and upright exercise, while the subjects of Sonnenblick et al (1965) exercised in the supine position only.

B-receptor block was obtained with pronethalol (nethalide), a forerunner of propranolol, in the studies of Chamberlain and Howard (1964), Schroder and Werko (1965) and Segel and Bishop (1965). Propranolol was the pharmacological agent used by Epstein et al (1965), and Sonnenblick et al (1965). It is doubtful if this difference alone could have influenced the results but dose for dose propranolol is ten times more potent as a B-receptor blocking agent than pronethalol (Black et al, 1964). However, no qualitative differences in the B-receptor blocking properties of the two drugs have been demonstrated so far (Black et al, 1964). More important

in this connection may be the route of administration. The drug was administered orally by Chamberlain and Howard (1964) and Schroder and Werko (1965) while all other workers have used the intravenous route.

The results reported by these workers are compared with those obtained in the present study in the course of the ensuing discussion.

The present author has also studied the effects of β -adrenergic block with propranolol on the haemodynamic response during static muscular work (sustained hand grip at 30% of the maximum voluntary contraction). Although this does not form a part of the present report attention will be drawn to some of the relevant observations made in that study. In this connection it may be pointed out that static muscular work is not associated with the "pumping effect" on venous return which is a feature of dynamic exercise. Furthermore, the vasodilatation in the exercising muscles is either absent or much less pronounced during static muscular work as compared to dynamic exercise.

B. Resting haemodynamic changes following β -adrenergic block:

Changes in the Systemic Circulation: The whole body oxygen uptake was not influenced by propranolol in the group as a whole, although in one subject (W.B., Fig.76) a significant reduction of 20% was observed. The reason for the decrease in oxygen uptake in this patient is not clear. The resting oxygen uptake did not alter significantly in the studies of Schroder and Werko (1965) and Segel and Bishop (1965).

The cardiac output at rest decreased by an average of 21.2% in the present study. This was associated with a significant reduction (17.3%) in heart rate but the stroke volume did not alter significantly. Similar results have been reported by Segel and Bishop (1965), Epstein et al (1965) and Sonnenblick et al (1965).

An increase in the resting mean aortic pressure was observed in all subjects in the present study. That the average value (9.9mm.Hg; 9.7%) did not achieve levels of statistical significance may well have been due to the small sample size.

There do not appear to be any comparable studies in the literature in which changes in the mean aortic pressure in resting subjects following the administration of propranolol have been reported. However, it has been reported that both propranolol and pronethalol when administered orally over a prolonged period produce a fall in blood pressure (Prichard, 1965). The same author also states that this hypotensive effect has not been observed when either drug is administered intravenously.

The systemic vascular resistance increased markedly in all subjects (average 40.3%). While this increase may have been due to reflex stimulation of the baroreceptors following the reduction in cardiac output, it is worthy of note that the mean aortic pressure consistently increased above the control resting values. The significance of this reflex "imbalance" is not understood at present.

A similar increase in the systemic vascular resistance is implied in the findings of other workers although they did not make specific comments on this finding (Segel and Bishop, 1965; and Sonnenblick et al, 1965).

Changes in the Pulmonary Circulation: A small increase in mean pulmonary artery pressure occurred in all subjects. The significance of this finding is difficult to evaluate. The changes in pulmonary vascular resistance were not consistent. In view of the marked increase in the mean pulmonary wedge pressure that was observed in these patients, the changes in mean pulmonary artery pressure may have been only passive in nature. The relative magnitudes of the changes in the two pressures (0.9 mm.Hg in

mean pulmonary artery pressure and 2.6 mm.Hg in mean pulmonary wedge pressure), would lend some support to this possibility.

There is only one other report in which the changes in pulmonary pressures following β -adrenergic block were studied (Segel and Bishop, 1965). These workers did not find any significant changes in either the mean pulmonary artery or the mean pulmonary wedge pressures.

The cardiopulmonary blood volume did not alter significantly after β -adrenergic block. There are no comparable studies in the literature in which changes in this variable have been measured.

The mean right atrial pressure increased in all four subjects but the average increase of 1.0 mm.Hg (40.0%) was not statistically significant. However the failure to demonstrate a significant increase may well have been due to the small sample size in the present study. Other workers have not reported on changes in this parameter.

Changes in left ventricular performance: For the group as a whole the average changes in left ventricular stroke work, mean stroke power index and mean ejection flow index were small and not statistically significant. However the mean pulmonary wedge pressure increased significantly, in two subjects (W.B. and J.G.). This would imply that myocardial contractility was depressed though to varying degrees in individual subjects. The maximum rate of pressure rise in the aorta decreased significantly in all subjects.

It has been claimed that the sympathetic "tone" in the supine resting subjects is minimal (von Euler, 1964; and Sonnenblick et al, 1965).

Sonnenblick et al (1965) have shown that β -adrenergic block depresses only minimally the velocity of fibre shortening in the resting supine human subject. They have interpreted this finding as indicating a low level of sympathetic activity in the supine position. The results from the present study are in accord with the findings of Sonnenblick et al (1965). Individual variations in the level of sympathetic activity during the supine posture may well account for the depression in myocardial contractility in the two subjects of the present study. However, formal proof of this hypothesis is still awaited.

The left ventricular minute work decreased significantly in all four subjects. Variable changes were seen in the systolic minute pressure-time index indicating that myocardial oxygen uptake did not alter significantly. For the group as a whole the diastolic minute pressure-time index did not change significantly. It is not possible to draw any conclusions about the possible changes in coronary blood flow since vasomotor activity of the coronary vessels is under the influence of β -receptors (Ahlquist, 1948; and Klocke et al, 1965). The last-named authors have also shown that myocardial oxygen uptake in dogs is not affected by β -adrenergic block.

C. Comparison of the haemodynamic changes during supine leg exercise before and after β -adrenergic block:

Since identical levels of oxygen uptake (Figs. 76 and 90) were achieved at each of the two levels of exercise the effect of β -adrenergic block on the haemodynamic response to exercise can be assessed with confidence.

Previous reports have tended to suggest that the oxygen uptake at the same exercise load is reduced after β -adrenergic block (Schroder

" and Werko, 1965; Epstein et al, 1965). However, during mild or submaximal levels of exercise Epstein et al (1965) did not find any difference in the oxygen uptake before and after the administration of propranolol. On the other hand, these workers reported a 40% reduction in the endurance time of maximal exercise and also a 6% decrease in oxygen uptake at this level of exercise. In the present study the exercise load was relatively mild even during exercise 2.

Changes in the Systemic Circulation: The cardiac output increased during exercise after β -adrenergic block, but the absolute level achieved during each of the two levels of exercise was much lower than the corresponding values during the control period. During exercise 1 the cardiac output during the control period averaged 4.98 l./min./sq.m. while after the administration of propranolol this was only 3.80 l./min./sq.m. The corresponding values during exercise 2 were 5.86 and 4.88 l./min./sq.m. respectively. Thus during exercise 1 and 2 after β -adrenergic block the cardiac output was 23.7% and 16.7% lower than that during the corresponding control periods. Since the oxygen uptakes were the same, the oxygen extraction per unit of the circulating blood increased in all subjects (Fig. 96).

The results of regression analysis shown in Fig. 94 indicate that the rate of increment in cardiac output per unit increase in oxygen uptake during exercise after β -adrenergic block was significantly lower than that during the control period ($p < 0.001$). That the percentage increments in cardiac output before and after the administration of propranolol were not significantly different (Fig. 90) is simply because of the lower starting level of cardiac output (resting cardiac output) after the drug.

Other workers have also reported a similar reduction in the cardiac output response during dynamic exercise following β -adrenergic block (Epstein et al, 1965; Segel and Bishop, 1965; and Sonnenblick et al, 1965).

Both the heart rate and stroke volume also increased during exercise performed after β -adrenergic block, but again the absolute values of the two measurements were lower as compared to the corresponding observations during the control periods (Fig. 96). It will be recalled that β -adrenergic block did not affect the resting stroke volumes while the heart rate decreased consistently.

Although the difference between the percentage increases in stroke volume during either level of exercise before and after β -adrenergic block were not statistically significant (Fig. 90), the results of regression analyses revealed that the rate of increment in stroke volume during exercise was significantly ($p < 0.05$) lower after β -adrenergic block as compared with the control observations (Fig. 94). On the other hand, the rate of increment in heart rate during exercise was not influenced by β -adrenergic block (Fig. 94), but since the resting heart rates were lower after the administration of propranolol the percentage increase in heart rate was significantly greater after the drug as compared with the changes during the control period. Thus β -adrenergic block did not influence quantitatively the heart rate response to exercise while the increase in stroke volume was significantly reduced.

It is of interest in this connection to note that during static muscular work (sustained hand grip) a marked increase in cardiac output, which is largely rate-dependent, is invariably observed. Following β -adrenergic block the cardiac output response is reduced but the

proportionate increase in heart rate is greater as compared with the control contraction (Macdonald et al, 1966). Thus it appears that the heart rate response during both dynamic and static exercise is at least in part due to vagal inhibition which may even be enhanced (compensatory response) following β -adrenergic block. Total cardiac denervation in animals, on the other hand, abolishes the heart rate response to exercise completely, the increase in cardiac output being entirely due to a marked increase in stroke volume (Bruce et al, 1963).

The systemic vascular resistance decreased during exercise after β -adrenergic block, but at each level of exercise it was significantly higher than during the corresponding control period (Fig. 98), thus enabling the blood pressure to be maintained even with a relatively reduced cardiac output. Remensnyder et al (1962) have shown that the vasodilatation in exercising muscles is not influenced by stimulation of the sympathetic innervation of these vessels. That being so, the relatively increased systemic vascular resistance during exercise after β -adrenergic block was presumably due to increased vasoconstriction in other regional vascular territories. This would suggest that the background sympathetic activity during exercise was greater after β -adrenergic block, due, presumably, to an attempt by the organism to overcome the effects of the pharmacological intervention.

Changes in the Pulmonary Circulation: The significance of the relatively greater increase in the mean pulmonary artery pressure during exercise after the administration of propranolol, is difficult to judge. The changes in pulmonary vascular resistance were variable, increasing during the lighter exercise load and decreasing during the heavier load of exercise. With the available information it is not possible to arrive

at any firm conclusions with regard to the changes in the vasomotricity of the pulmonary vasculature. However, in view of the varied changes observed it seems more likely that no active vasomotor changes occur as a result of β -adrenergic block. It is quite possible that the increase in the mean pulmonary artery pressure was related to the marked elevation in the mean pulmonary wedge pressure that occurred in all four subjects.

The relatively greater increase in the mean pulmonary wedge pressure after the administration of propranolol is, in the author's opinion, a significant finding. Since the oxygen uptake, and presumably ventilation, were identical before and after β -adrenergic block, this observation probably reflects, fairly faithfully, the changes in the "effective" (transmural) end-diastolic pressure in the left ventricle (Chapter : III).

The difference between the slopes of the two regression lines showing changes in mean pulmonary wedge pressure during exercise (Fig.95) is worthy of note. After β -adrenergic block the mean pulmonary wedge pressure was consistently elevated and the increase during exercise was along a steeper slope ($p < 0.05$).

Segel and Bishop (1965) also observed a relatively greater increase in the mean pulmonary wedge pressure during supine leg exercise after the administration of pronethalol.

The relatively greater, though statistically insignificant, increase in the cardiopulmonary blood volume during exercise after β -adrenergic block may well have been due to the larger end-diastolic volume of the left ventricle as reported by Sonnenblick et al (1965) in similar circumstances and previously referred to.

Although the increase in the mean right atrial pressure during exercise was greater after β -adrenergic block this did not achieve levels

of statistical significance (Fig. 91) probably because of the small sample size. Variable changes in the central venous pressure can also be seen in the data of Epstein et al (1965) although the authors did not comment on the findings.

Changes in Left Ventricular Performance: The small but significant increase in left ventricular stroke work observed during exercise after β -adrenergic block was comparatively less than the similar increase during the control period (Fig. 92). This is also seen in Fig. 95 where the slope of the post-propranolol regression line is significantly depressed ($p < 0.05$) as compared with the control regression. In the same figure the slope of the regression line for pulmonary wedge pressure shows the opposite change. The inference from these observations is that left ventricular performance is markedly depressed as a result of β -adrenergic block.

The changes in the mean pulmonary wedge pressure have been related to changes in left ventricular stroke work, and mean stroke power index in Figs. 99 and 100 respectively. These curves are comparable to the ventricular function curves of Sarnoff (Chapter: I). It is apparent from the diagrams that in each instance the ventricular function curve is shifted down and/or to the right, thus demonstrating a marked decrease in myocardial contractility following the administration of propranolol.

Similar conclusions have been arrived at by Sonnenblick et al (1965) who have demonstrated that the augmentation of the instantaneous velocity of shortening of the ventricular muscle during exercise is markedly diminished by propranolol. During the control exercise the instantaneous velocity of shortening (at the iso-length point) increased by an average of 69% but after β -adrenergic block only a 10% increase was

CHANGES IN STROKE WORK AND MEAN PULMONARY WEDGE PRESSURE DURING TWO LEVELS
OF SUPINE LEG EXERCISE BEFORE AND AFTER β -ADRENERGIC BLOCK

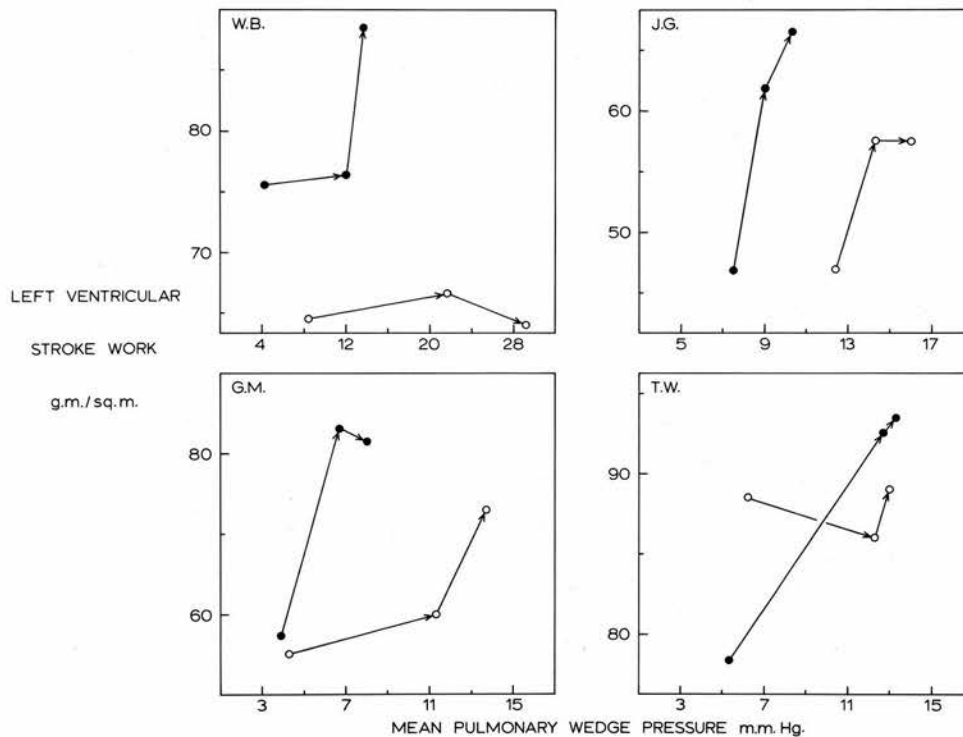


Figure 99

The changes in stroke work and mean pulmonary wedge pressure during supine leg exercise before and after β -adrenergic block in each of the four normal subjects. Only the average values of each period of observations are shown. Solid circles represent observations before, and open circles observations after β -adrenergic block. These lines represent the "ventricular function curves" of individual subjects. A shift of the line downwards and to the right indicates depression of myocardial contractility.

CHANGES IN MEAN STROKE POWER AND MEAN PULMONARY WEDGE PRESSURE DURING TWO LEVELS
OF SUPINE LEG EXERCISE BEFORE AND AFTER β -ADRENERGIC BLOCK

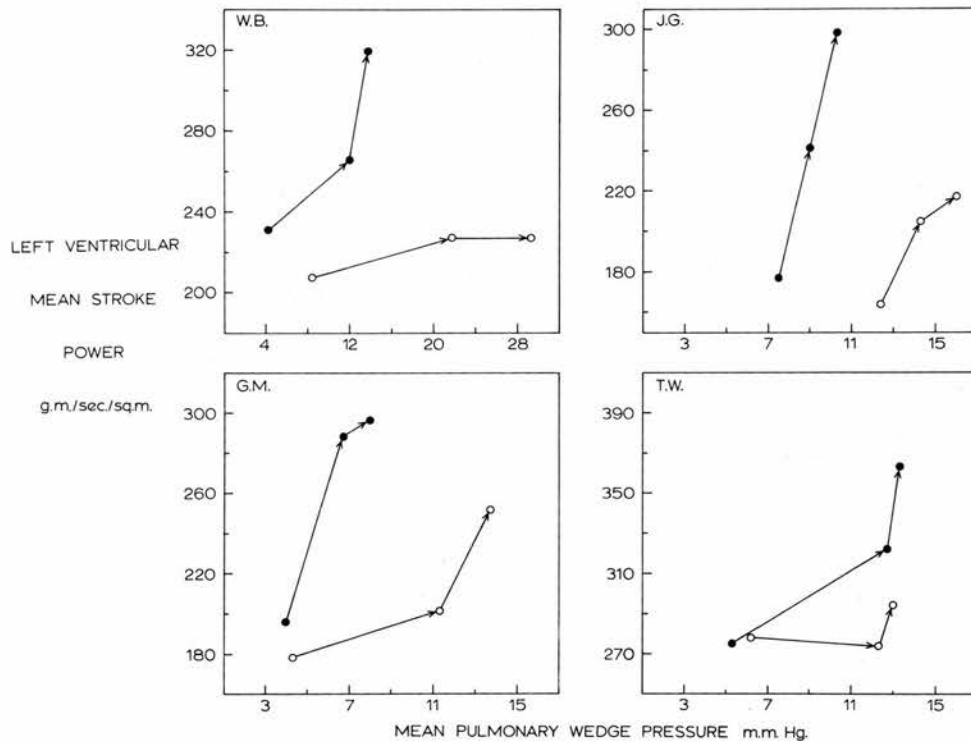


Figure 100

The changes in mean stroke power index and mean pulmonary wedge pressure during supine leg exercise before and after β -adrenergic block in each of the four normal subjects. Only the average values of each period of observations are shown. Solid circles represent observations before, and open circles observations after β -adrenergic block. These lines represent the "ventricular function curves" of individual subjects. A shift of the line downwards and to the right indicates depression of myocardial contractility.

observed. Instantaneous velocity of shortening at the same force (intraventricular pressure) provides a measure of the contractile element velocity. Such force-velocity relationships have been shown to define more precisely the contractile state of muscle (Chapter: I). An increase in the velocity of shortening represents increased myocardial contractility and vice versa.

Sonnenblick et al (1965) have also shown that the ventricular end-diastolic volume, which normally decreases even during supine leg exercise, fails to do so after β - adrenergic block. Thus the same or increased stroke volume and stroke work are produced from a larger initial fibre length (volume) after the adrenergic inotropic effect on the heart has been blocked. In this situation the heart conforms with the "Frank-Starling Law" and any increase in stroke volume is produced from a larger end-diastolic volume. Bruce et al (1963) have also shown a similar increase in the end-diastolic volume of the completely denervated heart in dogs. In this situation stroke volume is entirely a function of the end-diastolic volume.

These studies, including the present one, once again emphasise the importance of the sympathetic system in the regulation of myocardial performance. During exercise the reduction in the end-diastolic and end-systolic volumes of the ventricle is due entirely to adrenergic stimulation. It has now been convincingly demonstrated that an increase in heart rate per se does not affect the contractile properties of the heart muscle nor does this in itself result in an increase in the cardiac output (Sonnenblick et al, 1965; Stein et al, 1966; Benchimol and Liggett, 1966; and Sonnenblick et al, 1966). For the cardiac output to increase during exercise it is essential that myocardial contractility should also

be concomitantly augmented with the increase in heart rate. Under the influence of adrenergic stimulation during exercise the heart is able to produce an equivalent stroke volume from a reduced end-diastolic volume.

Sonnenblick et al (1965) have also produced evidence demonstrating that the "Frank-Starling" mechanism is in operation even during exercise. On pacing the human heart, with the subject at rest, they have demonstrated that the end-diastolic volume of the ventricle is markedly reduced but that this is associated with a decrease in stroke volume since the cardiac output is not altered significantly. Following exercise with the heart paced at the same rate as previously, the end-diastolic volume now increases and the stroke volume is restored to the normal resting value or may even increase. Thus the fact that exercise does not result in a reduction in the stroke volume, is in itself evidence that with a constant neuro-humoral background ventricular performance is a direct function of the end-diastolic fibre length (volume). The climate of opinion thus appears to have turned a full cycle with the "Frank-Starling" Law re-established as the fundamental mechanism that regulates myocardial performance. All other influences only help to modify the background but do not influence the structure.

The effect of B-adrenergic block on the changes in left ventricular minute work during exercise was similar to the effect on cardiac output (Figs. 94 and 95). Thus while the left ventricular minute work increased during exercise after B-adrenergic block, this was along a much flatter curve as compared to the similar changes during the control period.

The increase in systolic minute pressure-time index during exercise suggests an increase in myocardial oxygen consumption. Whether

β -adrenergic block resulted in any significant changes in the myocardial oxygen consumption, cannot be judged from the available data.

In the absence of knowledge about the changes in coronary vascular resistance the diastolic minute pressure index does not provide any useful information with regard to the possible changes in coronary blood flow.

There do not appear to be any studies in the literature so far bearing on the effect of β -adrenergic block on the changes in myocardial oxygen consumption and/or coronary blood flow during exercise in man.

SUMMARY AND CONCLUSIONS

The present investigation was undertaken to study the haemodynamic changes during supine leg exercise and the effect of β -adrenergic block (with propranolol) on these. Each of the four normal subjects performed supine leg exercise at two work levels both before and after the intravenous administration of propranolol. The oxygen uptake during the corresponding levels of exercise was the same before and after β -adrenergic block.

The haemodynamic changes during graded (two levels) supine leg exercise were similar to the observations of most other workers. A formal comparison with some of the published reports has been made.

In the resting supine posture the administration of propranolol (10 mg.) was followed by a significant reduction in the cardiac output and heart rate but without any significant change in the stroke volume. The mean aortic pressure increased in all subjects due to a marked increase in the systemic vascular resistance. The changes in pulmonary circulation were small and probably only passive in nature. Although

in two subjects the indices of left ventricular performance suggested a decrease in myocardial contractility (same stroke work with elevated mean pulmonary wedge pressure) this could not be said for certain in the other two subjects.

β -adrenergic block with propranolol was found to modify the haemodynamic response to supine leg exercise performed at the same work loads as during the control period.

The cardiac output response was markedly reduced but the heart rate response did not appear to be affected. The possible role of vagal inhibition in the heart rate response to exercise has been discussed.

Propranolol did not produce any marked changes in the pulmonary circulation either at rest or during exercise. A small increase in the mean pulmonary artery pressure was observed and it has been suggested that this may well have been due to the increase in the mean pulmonary wedge pressure. The latter increased both at rest and during exercise (marked increase during exercise) as compared to the pressure during the corresponding control periods.

Evidence has been presented to show that propranolol depresses left ventricular performance and this is most marked during exercise.

In view of the findings from the present study and some of the reports of other workers it has been concluded that adrenergic stimulation is an important mechanism in the regulation of cardiac function particularly during exercise. However, it has been argued that this is not the sole mechanism, but that adrenergic stimulation provides an "improved" background against which the "Frank-Starling" Law operates to regulate ventricular function.

APPENDIX

A P P E N D I X

COMMENTS ON THE STATISTICAL METHODS USED

1. Test for the significance of difference between two positively correlated variates

In Chapter III the comparison of beat by beat changes in the pulmonary wedge and left ventricular end-diastolic pressures has been carried out by treating the difference between individual pairs of observations as a random variable. The significance of departure from zero of the mean difference was then estimated by the standard formula (Fisher, 1958):

$$t = \frac{\bar{x}_d}{\sqrt{s^2/n}} \quad \text{for } (n-1) \text{ degrees of freedom}$$

where \bar{x}_d = Mean difference

s^2 = Variance about this mean

n = Number of pairs of observations

This is a more stringent test than a comparison between the mean values of each variate by the more conventional form of the 'Student's' t test (vide infra) since the degrees of freedom are almost halved. However, this test is particularly suitable when paired observations are compared, as in this case.

The same form of analysis was used in Chapter V when assessing the significance of difference between the percentage deviation (during exercise) from the mean of the resting values before and after β -adrenergic block; the values for each identical period of exercise in individual subjects being treated as paired observations. This was considered justified particularly in view of the fact that observations were made on the same individual and at equivalent loads of exercise.

2. Test to compare the means of two sets of observations on the same parameter (Chapters: IV and V)

This was done with the help of the 'Student's' t test using conventional formulae (Fisher, 1946).

In each instance the significance of difference between the variances of the means of the two sets of observations was assessed by Snedecor's 'F test' (Snedecor, 1956) when the difference between these variances was not significant the value for t was accepted as such.

In cases where the variances of the two means were significantly different one of the two following approaches was followed.

i. The degrees of freedom used for assessing the significance of the 't' value were corrected as follows (Bailey, 1959):

$$\text{d.f. (Degrees of freedom)} = \frac{1}{\frac{u^2}{n_1-1} + \frac{(1-u)^2}{n_2-1}}$$

$$\text{where } u = \frac{S_1^2/n_1}{S_1^2/n_1 + S_2^2/n_2}$$

and S^2 = variance of the mean

ii. The alternative approach suggested by Fisher is that of Behren's test (Fisher and Yates, 1963) which takes into account the ratio of the standard errors of the two means.

$$s_1/s_2 = \tan \phi$$

s = standard error of the mean

Tables are available in which the significance of the value of 't' obtained from standard formulae is related to ϕ , the tangent of which is obtained as above.

The second method (ii) was only occasionally used.

3. Correlation and Regression analyses (Chapters III and V)

These were performed using standard formulae (Bailey, 1959).

The slopes of the regression lines (regression coefficients) were also compared by the 'Student's' t test using a pooled estimate of the standard errors of the regression coefficients.

The constants (intercepts) were also similarly compared.

4. The analysis of variance (Chapter IV)

The analysis of variance used in Chapter IV was designed in the form of a 'two-factor' analysis, i.e. one of the post drug periods was each time compared with the control period. Both the number of patients in the two blocks (periods) and the number of replications in each block were the same. However, the number of replications were usually different in the two blocks.

The variances of the data were partitioned as follows:

- i) Between patients
- ii) Between treatments
- iii) Interaction (Patient x Treatment)
- iv) Residual

The significance of the between treatments variance estimate was then judged by comparing it with the residual (or error) variance estimate by the F test.

The interaction variance estimate was usually significant, indicating lack of homogeneity in the response to treatment. However, in the interpretation of the results major emphasis was placed on the between treatment and the residual variance estimates.

A part of the statistics, in particular the analysis of variance, was worked out with the help of a computer.